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THE ACID-BASE STATUS OF HUMAN INFANTS IN RELATION TO BIRTH ASPHYXIA AND THE ONSET OF RESPIRATION

L. S. JAMES, M.B. (N.Z.), I. M. WEISBROT, M.D.,* C. E. PRINCE, M.D.,**
D. A. HOLADAY, M.D., AND V. APGAR, M.D.
NEW YORK, N. Y.

EARLIER studies[1] have led to the conclusion that respiratory failure in the newborn is due to anoxia. The aim of the present study has been to evaluate the birth status of the infant and to time the onset of respiration in relation not only to the arterial oxygen saturation but also to the carbon dioxide tension (P_{CO_2}), the pH, and the total available buffer. Although the pH and pCO_2 have been measured previously,[2-5] they have not been considered as reflecting the duration of an episode of asphyxia. The term "asphyxia," as defined by Schmidt,[6] has been adopted since it denotes a simultaneous decrease both in the intake of oxygen and the elimination of carbon dioxide, i.e., anoxia plus hypercapnea. The way in which hypoventilation or asphyxia changes these variables, producing first a respiratory acidosis followed by a superimposed metabolic acidosis,[6-11] has been extensively reported in animals and adults.

From the Anesthesiology Service, The Presbyterian Hospital, Sloane Hospital for Women, Babies Hospital, Departments of Anesthesiology, Obstetrics and Gynecology and Pediatrics, Columbia University, College of Physicians and Surgeons, New York 32, New York.

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*Edan Ros and Public Health Research Fellow.

**Macy Foundation Fellow.

MATERIAL AND METHODS

Blood samples were obtained from the artery and vein in a clamped segment of the umbilical cord at the moment of delivery. The samples were collected in greased syringes, the dead spaces of which were filled with a concentrated heparin solution.

Analysis of the samples for oxygen, carbon dioxide, oxygen capacity,[12] pH,[13] and hematocrit[14] was performed as soon after collection as possible, usually within 2 hours, the samples being rotated in iced water. The majority of oxygen saturations were measured by a manometric method.[12] Several bloods were analyzed with the double scale cuvette oximeter[15] or by the method of Nahas using the Beckman spectrophotometer.[16] All three methods were standardized against the manometric analysis of Van Slyke.[17] The microgas analysis was found to vary by ± 1 per cent[12] while

the standard deviation of the differences was for the Beckman ± 1.3 per cent over the entire range, and for the cuvette oximeter ± 2 per cent over 40 per cent saturation and ± 3.5 per cent below 40 per cent.

The Pco_2 and buffer base (BB) were calculated from the Singer and Hastings nomogram[17] using the pH, the CO_2 content, and the hematocrit. The term "buffer base" refers to the total available buffer and includes both the bicarbonate (or alkali reserve), the protein, and the hemoglobin. In the study of metabolic acidosis, it is a more valuable measurement than the bicarbonate alone.

The recent work of Dawes and associates,[18] on the fetal circulation, indicates that the umbilical artery blood represents the blood going to the fetal tissues and not fetal venous blood. Contrary to earlier studies by Barcroft and his associates[19, 20] and Huggett,[21] the blood supplying the brain contains only slightly more oxygen than that in the umbilical artery (Fig. 1).[22] The more accurate interrelationship of the oxygen saturations in the various vessels was obtained by withdrawing blood from eight major vessels simultaneously rather than using discrete samples collected over a period of time. Since the cineangiographic evidence of Lind and Wegelius[23] suggests that the fetal circulation in the human being resembles that in the lamb, the umbilical artery has been taken to represent the blood supplying the tissues of the infant at the moment of delivery.

One minute after the complete birth of the infant, he was evaluated and given a score.[24] Two points were given for each of the following: color, respiration, muscular tone, nasal irritability, and heart rate. All the infants with a score of 8, 9, or 10 are vigorous and have breathed within seconds of delivery. In this group, scores less than 10 have reflected a lower score for color. The infants with a score of 4 or less are blue and limp and have failed to establish respiration by one minute. With increasing depression the last two vital signs, reflex irritability and heart beat, disappear, in that order.

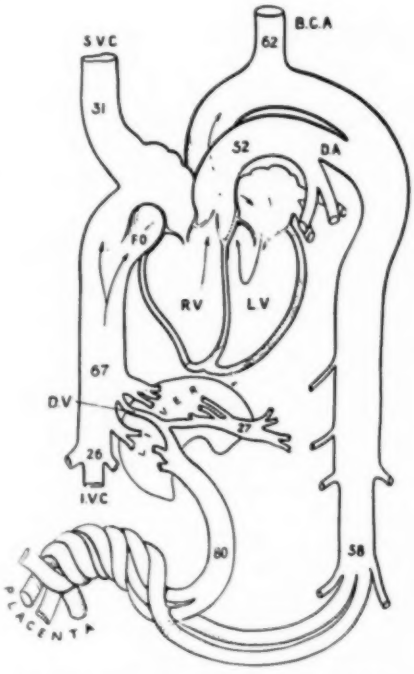

Fig. 1.—Diagram of the fetal circulation. The figures indicate the percentage oxygen saturation of blood withdrawn simultaneously from various vessels, and averaged from determinations on 6 lambs. I.V.C., inferior vena cava; S.V.C., superior vena cava; D.V., ductus venosus; F.O., foramen ovale; D.A., ductus arteriosus; B.C.A., brachiocephalic artery. (*From* Changes in the Heart and Lungs at Birth, Cold Spring Harbor Symposia on Quantitative Biology, Vol. XIX, 1954.)

The time required for the infant to establish spontaneous and continuous respirations is termed, "time to sustained respiration." (T.S.R.)

To determine the biochemical status of the depressed group, samples from either the umbilical artery, the portal vein area in the liver, or from the right or left atria have been used. This has been considered justifiable for several reasons. In many of these infants the heart rate is slow and the pulse feeble. The blood pressure has not yet been measured at this time, but from the response of infants 2 to 11 days old[25] and from that of newborn and fetal lambs[26] to severe anoxia, it is likely to be low. Therefore, the cord circulation will be poor, especially if there is compression. Frequently, the cord is collapsed and bloodless or the blood is present in loculated sections between areas of complete occlusion. In such cases, a sample of the circulating blood from the infant, either arterial or venous, if obtained before the onset of respiration, will give a more reliable indication of his condition. All the portal vein samples were obtained during resuscitation (artificial expansion of the lungs under positive pressure) about the time the first spontaneous breath was taken. Consequently, the oxygen level will be higher, the Pco_2 somewhat lower, and the pH higher than prior to the resuscitation. However, the BB, which returns to normal relatively slowly, may be expected to indicate more accurately the severity of the asphyxia.

RESULTS

The biochemical analyses of the umbilical cord blood of 101 babies are presented in Table I and Figs. 2 and 3. The data have been arranged according to the type of delivery (vaginal or section) and the Apgar score of the infant at one minute.

There is a wide range in the oxygen levels in both the umbilical artery and vein blood and in the A-V difference. All the infants exhibited some degree of asphyxia with a low oxygen saturation and a high CO_2 tension. Of the 63 umbilical artery samples, 26 had an oxygen saturation below 10 per cent and 7 had no measurable oxygen. Fourteen of these severely anoxic infants were not depressed (score 8 and 9) and cried spontaneously within seconds of delivery (Fig. 2). Four were in the intermediate group (score 5 to 7) and 8 were in the depressed group (score 0 to 4). The highest umbilical artery oxygen saturation recorded was 51 per cent.

The umbilical artery pH ranged from 7.00 to 7.35, with a mean of 7.26 for the vigorous and 7.14 for the depressed infants. The Pco_2 ranged from 39 to 98 mm. Hg, with a mean of 55 for the vigorous and 74 for the depressed infants, indicating a respiratory acidosis.

A depression of the BB below the normal of 42 mEq./L. for pregnant women (normal for adult males 47 to 50) revealed the presence of a superimposed metabolic acidosis in a number of instances (Fig. 3).

A comparison has been made between the pH, and Pco_2, and BB in either portal vein or umbilical artery blood in the depressed infant and umbilical artery samples from the vigorous group (Table II). Both the pH and BB are significantly lower while the Pco_2 is significantly higher in the depressed infants. $p < .01$. The severe degrees of metabolic acidosis

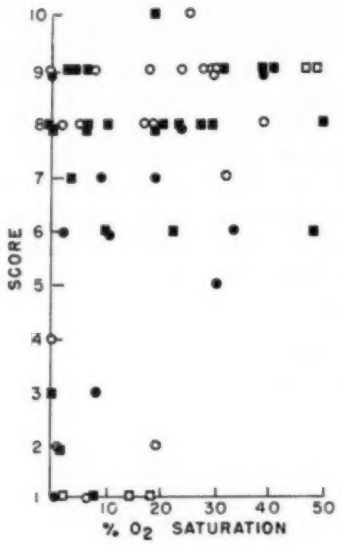

Fig. 2.

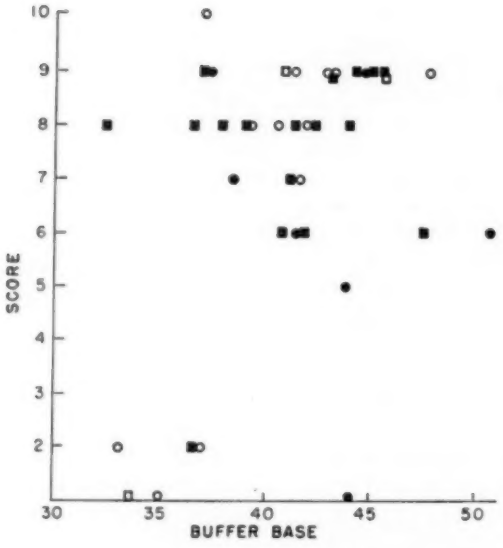

Fig. 3.

Figs. 2 and 3.—○ Vaginal delivery—regional anesthesia; ● Vaginal delivery—inhalation anesthesia; ■ Cesarean section—regional anesthesia; □ Cesarean section—inhalation anesthesia.

Fig. 2.—Umbilical artery—oxygen saturation. Comparison of clinical status of infant at birth with arterial oxygenation.

Fig. 3.—Umbilical artery—buffer base. Comparison of clinical status of infants at birth with arterial buffer base.

TABLE I. BIOCHEMICAL FINDINGS IN THE UMBILICAL ARTERY AND VEIN

NO.	NAME	SCORE	OXYGEN % SAT. ARTERY	OXYGEN % SAT. VEIN	pH A	pH V	P_{CO_2} MM. HG A	P_{CO_2} MM. HG V	BB mEQ./L. A	BB mEQ./L. V	ANESTHESIA AND COMPLICATIONS
		8-10			*Regional Anesthesia*			*Vaginal Delivery*			
1	Lo	9	0	24	7.32	7.42	45	39	41	46	None
2	Mo	8	2	29	7.19	7.27	62	50	39	41	Spinal
3	Bur	8	6	68	–	7.20	–	45	–	37	None
4	Vel	8	7	67	–	–	–	–	–	–	Caudal
5	Sc	9	9	–	7.26	–	59	–	43	–	Pudendal
6	Irv	9	–	30	–	–	–	–	–	–	Saddle
7	Thos	10	–	45	–	7.24	–	39	–	42	Pudendal
8	Pier	8	17	59	7.20	7.28	63	49	41	42	Pudendal
9	Bal	9	19	48	–	7.40	–	42	–	47	Spinal
10	Me	8	19	64	–	7.27	–	40	–	37	Epidural
11	Yo	9	25	34	–	–	–	–	–	–	None
12	Sant	9	28	–	7.31	–	48	–	43	–	Pudendal
13	Rod	9	30	–	7.37	–	47	–	48	–	Spinal
14	Jack	9	30	65	7.27	7.32	–	40	–	41	Pudendal
15	Jo	9	30	–	7.33	–	48	–	45	–	Caudal
16	Ha	10	31	61	7.15	7.20	64	49	37	37	Caudal
17	Wo	8	45	72	–	7.36	–	35	–	42	Caudal
Average			19.8	47.6	7.26	7.29	54.5	42.8	42.1	41.2	
								Cesarean Section			
18	Jo	8	0	72	–	–	–	–	–	–	Spinal
19	Do	8	0	23	–	–	–	–	–	–	Spinal
20	Hi	9	3	15	–	–	–	–	–	–	Spinal
21	Ro	9	5	12	7.30	7.41	50	36	43	45	Spinal
22	Ca	9	6	9	–	7.17	–	69	–	39	Spinal
23	Sch	9	7	29	7.10	7.22	64	46	37	38	Spinal
24	Lev	8	7	10	–	–	–	–	–	–	Spinal
25	Tr	8	11	23	7.10	7.12	77	69	36	36	Spinal
26	Mi	10	19	72	–	–	–	–	–	–	Spinal
27	Rod	8	19	30	7.14	7.19	81	70	38	39	Spinal
28	Sh	8	–	13	–	7.24	–	63	–	43	Spinal
29	Fo	9	–	40	–	7.26	–	50	–	41	Spinal
30	Ri	8	–	41	–	7.20	–	57	–	39	Spinal
31	Ha	10	–	72	–	7.20	–	51	–	39	Spinal
32	Mag	8	21	44	7.22	7.29	54	43	39	40	Spinal
33	Lo	8	24	53	7.27	7.31	53	41	42	41	Spinal
34	Sc	9	–	31	–	–	–	–	–	–	Spinal
35	Bur	8	28	67	7.27	7.29	50	43	41	41	Spinal
36	Ri	8	30	32	7.04	7.17	74	51	32	35	Spinal
37	Pr	9	32	65	7.33	7.35	51	44	45	45	Spinal
38	Reu	9	32	51	7.26	7.29	59	51	44	43	Spinal
39	Men	9	39	70	7.30	7.36	54	45	45	45	Spinal
40	Ra	9	41	62	–	–	–	–	–	–	Spinal
41	O'R	8	51	79	7.33	7.37	45	37	44	45	Spinal
Average			19.7	42.3	7.22	7.26	59.3	50.9	40.5	40.8	
					Inhalation Anesthesia			*Vaginal Delivery*			
42	Rei	9	0	34	7.33	7.37	59	45	37	39	Cyclopropane
43	Rad	8	25	67	7.26	7.33	–	–	–	–	Cyclopropane
44	Da	9	39	65	–	7.28	–	47	–	41	Cyclopropane
45	Go	8	–	–	7.25	7.25	49	47	42	41	Cyclopropane
46	Li	8	–	44	–	–	–	–	–	–	Cyclopropane
47	New	8	–	47	–	–	–	–	–	–	Cyclopropane
48	Deigh	10	–	62	–	7.31	–	46	–	–	Cyclopropane
49	May	8	–	63	–	7.30	–	46	–	–	Cyclopropane
50	Kr	8	–	68	–	–	–	–	–	–	Cyclopropane
51	Ga	9	–	69	–	7.46	–	–	–	–	Cyclopropane
52	Meu	8	–	68	–	–	–	–	–	–	Cyclopropane
53	Ro	9	–	75	–	7.33	–	49	–	–	Cyclopropane
54	Mo	9	–	79	–	7.46	–	32	–	47	Cyclopropane
Average			21.3	61.7	7.28	7.35	54	44.5	39.5	42.0	

TABLE I—CONT'D

NO.	NAME	SCORE	OXYGEN % SAT. ARTERY	OXYGEN % SAT. VEIN	pH A	pH V	P_{CO_2} MM. HG A	P_{CO_2} MM. HG V	BB MEQ./L. A	BB MEQ./L. V	ANESTHESIA AND COMPLICATIONS
											Cesarean Section
55	Ch	9	48	78	7.27	7.31	49	42	41	42	Cyclopropane
56	Ru	9	49	85	7.30	7.35	52	48	45	46	Cyclopropane
Average			48.3	81.5	7.28	7.33	50.5	44.9	43.2	43.9	
											Inhalation Anesthesia Vaginal Delivery
57	To	8	9	29	7.28	7.33	46	40	41	42	N_2O
58	Br	8	–	26	–	–	–	–	–	–	N_2O
59	Ha	8	18	30	7.20	7.26	–	–	–	–	N_2O
60	Va	9	–	45	–	7.33	–	50	–	46	N_2O
61	Camp	8	23	–	7.33	–	51	–	47	–	N_2O
62	Men	9	44	–	7.40	–	39	–	46	–	N_2O
63	Pier	8	–	81	–	7.29	–	–	–	47	N_2O
Average			23.5	42.2	7.30	7.30	45.3	45	44.6	45.0	
		5-7									*Regional Anesthesia Vaginal Delivery*
64	Dur	6	–	35	–	7.25	–	55	–	42	Pudendal
65	Mil	7	33	56	7.36	7.45	39	32	42	44	Caudal
66	DeJ	6	–	57	–	7.28	–	48	–	–	Caudal
67	Ray	5	–	61	–	7.37	–	43	–	–	Caudal
Average			33	52.2	7.36	7.33	39	44.5	42	43	
											Cesarean Section
68	Beau	7	4	31	7.21	7.33	67	45	41	43	Spinal
69	Aiel	6	10	32	7.22	7.33	64	43	42	42	Spinal
70	Beas	6	23	30	7.16	7.23	69	57	41	41	Spinal
71	Ortiz	6	48	84	7.39	7.39	44	40	47	47	Spinal
72	Ja	5	–	83	–	–	–	–	–	–	Sample before delivery
Average			21.2	52.0	7.24	7.32	61.0	46.2	42.7	43.2	
											Inhalation Anesthesia Vaginal Delivery
73	Gai	6	2	40	7.21	7.24	69	55	42	41	Cyclopropane
74	Mel	7	9	42	7.23	7.22	53	46	38	37	Cyclopropane
75	Gib	6	11	48	7.22	7.29	92	54	51	46	Cyclopropane
76	Val	7	19	37	7.25	7.28	–	–	–	–	Cyclopropane
77	Riv	5	30	47	7.23	7.26	67	56	44	44	Cyclopropane
78	Rei	7	–	49	–	–	–	–	–	–	Cyclopropane
79	Ley	7	–	54	–	7.36	–	39	–	43	Cyclopropane
80	Len	5	–	72	–	–	–	–	–	–	Cyclopropane
81	Kel	6	34	73	7.27	7.32	–	–	–	–	Cyclopropane
Average			17.5	51.3	7.23	7.28	70.2	50.0	43.7	42.2	
											Inhalation Anesthesia Cesarean Section
82	Pi	5	4	11	–	7.35	–	38	–	40	Cyclopropane
											Vaginal Delivery
83	Pa	7	14	24	7.23	7.23	56	54	43	43	N_2O
		0-4									*Regional Anesthesia Vaginal Delivery*
84	Gou	4	0	17	–	–	–	–	–	–	Caudal
85	Sun	2	1	9	7.01	7.03	99	93	33	34	Saddle
86	Bu	1	7	–	7.08	–	78	–	35	–	Caudal
87	Wa	1	–	21	–	7.28	–	57	–	43	Pudendal
88	Fried	2	19	34	7.18	7.25	57	46	37	39	4+ nucal cord with facial petechiae; spinal
Average			6.7	20.2	7.09	7.18	78.0	65.3	35.0	38.6	
											Cesarean Section
89	Per	3	0	10	–	–	–	–	–	–	Spinal
90	Em	2	1	41	7.17	7.20	63	53	38	38	Cord prolapse thru wound for 2 min.
91	Mer	1	7	63	–	–	–	–	–	–	Local and Pentothal
Average			2.6	38.0	7.17	7.20	63	53	38	38	

TABLE I—CONT'D

NO.	NAME	SCORE	OXYGEN % SAT. ARTERY	OXYGEN % SAT. VEIN	pH A	pH V	P_{CO_2} MM. HG A	P_{CO_2} MM. HG V	BB MEQ./L. A	BB MEQ./L. V	ANESTHESIA AND COMPLICATIONS
					Inhalation Anesthesia			*Vaginal Delivery*			
92	Ga	1	0	0	7.08	7.07	94	93	34	34	Cyclopropane
93	Ha	1	–	21	–	–	–	–	–	–	Cyclopropane
94	Br	3	15	51	–	7.27	–	61	–	46	Cyclopropane
95	Su	1	18	38	7.00	7.11	–	–	–	–	Ruptured uterus; Cyclopropane
Average			11.0	27.5	7.04	7.15	94	77.5	34	40	
								Cesarean Section			
96	Mul	1	0	62	7.32	7.37	53	40	44	44	{Cyclopropane }4+ nucal cord
97	Fent	3	8	27	7.32	7.38	–	–	–	–	Cyclopropane
98	Pier	2	–	29	–	7.33	–	44	–	43	Cyclopropane
Average			4	39.3	7.32	7.36	53	42	44	43.5	
								Vaginal Delivery			
99	Wa	1	–	42	–	7.07	–	71	–	33	Ether
100	Tr	1	–	67	–	7.25	–	49	–	41	Prolapsed cord; ether
101	Mer	3	–	56	–	7.26	–	50	–	41	Chloroform
Average				55		7.19		56.6		38.3	

and derangement of pH and P_{CO_2} which were observed as a result of prolonged apnea are illustrated in Table III and Fig. 4. Here the portal vein or atrial samples taken at the onset of respiration have been compared with the biochemical status of the cord blood when samples could be obtained. In all instances, the biochemical measurements in the portal vein blood showed a greater degree of asphyxia.

DISCUSSION

These studies have revealed the varying degrees of asphyxia which occur during all forms of delivery. Contrary to earlier reports,[1, 4, 5] an infant may make the initial respiratory gasps with no measurable oxygen in his arterial blood. In this sense, anoxia, as measured by the oxygen saturation of the umbilical artery's blood, correlates poorly with postnatal vigor. The significant difference which has been demonstrated between the vigorous and depressed infants lies in the pH, P_{CO_2}, and BB (Table II). Previous studies have shown that these variables give a measure of an asphyxial insult,[6-11] a brief period of asphyxia causing in the main a respiratory acidosis with a raised P_{CO_2} and little change in the BB. This pattern of change may be seen in the vigorous infants (score 8-10, Table I). If on the other hand, the asphyxia is prolonged, a marked reduction in the BB occurs (depressed infants score 0-4, Table I), indicating a metabolic acidosis which has become superimposed on the respiratory acidosis.

From this it is evident that the response of the infant to asphyxia is identical to that of the adult.[6-11] The rapid recovery after birth[29] also follows the adult pattern. In the vigorous infants the absence of a severe metabolic acidosis in the presence of a high P_{CO_2} indicates that the period of asphyxia has been quite brief. In

TABLE II. STATISTICAL COMPARISON OF VIGOROUS AND DEPRESSED INFANTS

	VIGOROUS INFANTS (SCORE 8-10) UMBILICAL ARTERY SAMPLES			DEPRESSED INFANTS (SCORE 0-4) UMBILICAL ARTERY OR PORTAL VEIN			
	NUMBER	MEAN	S.D.	NUMBER	MEAN	S.D.	p
O_2	43	22.2	21.77	12	6.3	7.3	
pH	30	7.26	0.085	10	7.04	0.142	$p < .01$
PCO_2	27	55.3	10.25	9	82.0	19.93	$p < .01$
BB	27	41.5	3.68	10	31.4	6.93	$p < .01$

TABLE III. BABIES SEVERELY DEPRESSED AT BIRTH

			CHANGES IN pH, P_{CO_2}, AND BB WITH TIME				
NAME	SCORE	SITE	OXYGEN % SATURATION	pH	P_{CO_2}	BB	
Fr	2	Umbilical artery	19.2	7.18	57.0	37.0	Spinal anesthesia, cord tightly round neck; facial petechiae; T.S.R.,* 3 min., 35 sec.
		Portal vein	21.2	6.98	90.2	30.5	P.V. sample 25 sec. after first spontaneous respiration
Fe	3 ↓	Umbilical artery	8.0	7.32			Anesthesia cyclopropane; thick meconium-stained mucus in pharynx
at 3 min.	1	Portal vein	50.9	7.10	77.0	37.8	T.S.R., 12 min.; P.V. sample 2 min. after first spontaneous respiration
Wa A Twins	1	Umbilical vein	41.9	7.06	70.5	33.2	Anesthesia chloroform; twins locked, 2 weeks premature; T.S.R., 25 min.
A		Portal vein	61.9	6.91	69.5	24.1	P.V. sample 2 min. after first spontaneous respiration
B	1	Portal vein	55.9	6.80	114.5	21.7	P.V. sample 1 min. after first spontaneous respiration
Ch	0	Left atrium	93.0	6.74	39.9	<15.0	Emergency section for prolapsed cord; no heartbeat at birth, cardiac massage Sample after 25 min. of artificial ventilation when infant took first spontaneous gasp

*T.S.R. = time from birth to spontaneous respiration.

light of this, earlier interpretations that the fetus is normally adjusted to these high tensions of carbon dioxide[27] can no longer be accepted.

The high score group of infants, those who were well oxygenated, had little or no depresion of the BB. Where the oxygen saturation was 10 per cent or less in this group, in all but one case the BB value was slightly below the average for the group but well above the average for the depressed infants. The low BB values occasionally seen in this group were associated in most instances with a second stage of labor of 2 hours or more or slowing and irregularity of the fetal heart during the first stage of labor. This undoubtedly reflects anoxia during labor which is sufficient to disturb metabolism but not enough to depress the infant significantly.

Several factors probably contribute to the asphyxia which appears to occur as a normal phenomenon in almost every delivery.

Cord Compression.—

Any reduction in the blood flow through the cord will lower the arterial oxygenation since the fetal venous blood (26 to 31 per cent saturated in the lamb[22]) will be passing directly into the arterial circulation with little or no mixing with oxygenated blood from the placenta. The saturation in the umbilical vein will remain unchanged[30] or may even be raised, since the fetal blood will remain in contact with the blood in the intervillous space for a longer period; but with reduction in flow, this blood does not reach the fetal circulation. The reduction in flow can be caused by kinking, prolapse, pressure between the fetus and the rim of the pelvis or vagina, or when the cord is wound tightly round the neck. Clemetson and Churchman[31] have shown the large difference in saturation between the umbilical artery blood and that in the vein, which may be found in this last situation. Manipulation of the cord causes constriction of the umbilical arteries, which in turn slows the stream of blood through the placenta. Barcroft[30] has vividly described the acute sensitivity of these vessels, particularly at term.

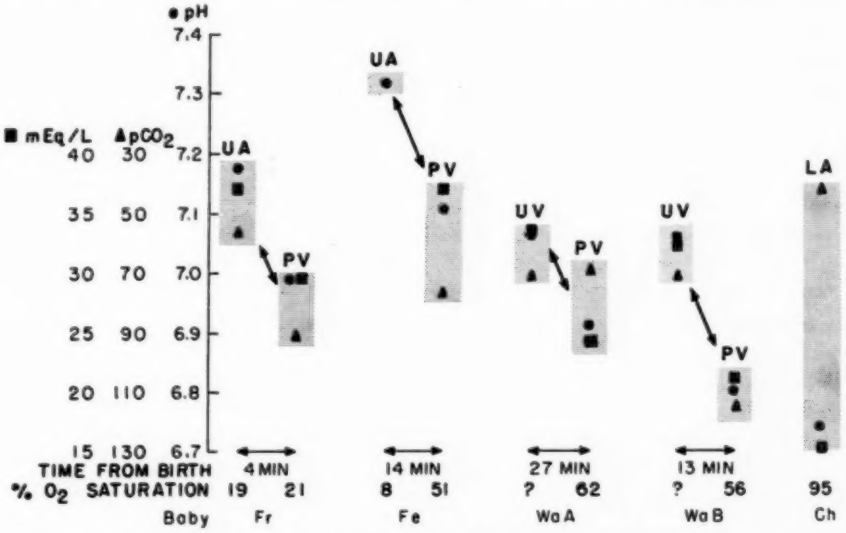

Fig. 4.—Changes in pH, pCO_2, and buffer base in 5 depressed newborn infants. UA—umbilical artery; UV—umbilical vein; PV—portal vein; LA—left atrium. The same umbilical vein sample has been used for comparison in twins Wa A and Wa B.

The values for Ch represent pure metabolic acidosis remaining after 25 minutes of resuscitation. The oxygen saturation in the LA was 99 per cent.

Changes in Uterine Blood Flow.—

a. *Posture:* The supine position has been shown to be associated with compresion of the mother's inferior vena cava by the heavy gravid uterus. Howard and his associates[32] have demonstrated that the pressure in the femoral vein may be raised from 108 to 239 mm. H_2O by this mechanism. This rise will decrease the pressure gradient between the uterine artery and vein and will tend to reduce blood flow through the uterus. When

the obstruction to the inferior vena cava is more complete, sufficient to cause hypotension in the mother,[33] an even greater reduction in flow will occur. This factor must be considered in cesarean section during which the mother may be flat on her back for 15 or 20 minutes before the baby is delivered. It is probable that the occasional very low oxygen value obtained in both cord vessels at cesarean section under local anesthesia is caused partly by this obstruction effect[34] (Table I).

b. *Hypotension with spinal anesthesia or maternal hemorrhage:* Hypotension not infrequently produced by spinal anesthesia will reduce the pressure gradient and the uterine flow. Fetal distress revealed by excessive movements or slowing of the fetal heart occurs under such conditions. Whether because of hypotension, increased uterine tonus, or some other factor as yet undetermined, the oxygen saturation in lambs delivered under spinal anesthesia is uniformly lower than in those delivered under pentobarbital.[35] Henderson reports a similar finding in human beings in comparing spinal and inhalation anesthesia.[36] Hypotension as a result of hemorrhage is likely to have an even more profound effect on reducing the uterine flow.

c. *Uterine contraction:* Caldeyro-Barcia[37] has shown that with a strong uterine contraction, blood flow through the uterus and placenta is completely arrested.

Uterine vein samples withdrawn a short time before delivery of the fetus by cesarean section[38] show, in most instances, a higher oxygen saturation than does umbilical vein blood obtained after delivery from a clamped segment of cord. This is contrary to the figures which Barron and Meschia[39] give in studies on the placental exchange of respiratory gases in the sheep and rabbit, and suggest that in the few minutes between the sampling from the uterine vein and delivery of the infant a reduction in oxygen transfer has occurred. Changes in the uterine circulation with manipulation, incision, and the immediate contraction which occurs as the amniotic fluid gushes out could account for this difference.

d. *Partial separation of the placenta:*

This will reduce the effective area of diffusion and will lead to a lower oxygenation of the fetus.

Reduction in the Maternal Exchange of Respiratory Gases.—

a. *Breath holding and straining:* Both of these occur during vaginal delivery, when anesthesia is not given or is minimal, and may result in a significant lowering of the maternal arterial oxygen saturation.

b. *Inhalation anesthesia:* The effect of inhalation anesthesia upon fetal oxygenation varies as much with the agent being used as with the clinic reporting the study. Good and poor results have been claimed for all agents. Because of a variety of techniques and the many additional factors noted above, it is difficult to determine the effect of the agent itself. However, if the mother has any airway obstruction during anesthesia, her CO_2 elimination and oxygen uptake will be impaired. This effect will be reflected in the fetus if delivery is prolonged.

It has been assumed by some authors that samples obtained at cesarean section under regional anesthesia represent normal in utero conditions in the

human being.[28] This has led to the concept of "Everest in utero" and to the belief that, with placental aging, fetal arterial oxygen saturation falls as term approaches.[40, 41] However, any sample obtained either at vaginal delivery or cesarean section is unlikely to represent the normal conditions before labor or operation since both uterine blood flow and cord compression cannot be controlled. The multiple factors enumerated above, acting separately or in combination, will all tend to lower the oxygenation of the fetus at delivery. While cord compression will increase the difference in saturation between the umbilical artery and vein, all the other factors will tend to lower the oxygenation of both vessels since they interfere with the exchange between mother and fetus. Undoubtedly, this accounts for the low average but the very wide range in published figures (10 to 60 per cent saturation in the umbilical artery and 10 to 84 per cent saturation in the umbilical vein[3-5, 28, 31, 34, 40-47] [Table IV]). The highest human figures reported are almost identical with the normal value which Dawes and associates[35] and Barron and Meschia[39] observed for lambs. These high values, rather than the average, probably give a truer indication of the normal in utero environment. Further indirect evidence which supports a high intrauterine oxygen environment is found in the color photographs of the unborn human infant taken by means of hysterophotography.[48] Here the infant actually appears to be pink.

An interesting advance has been the development of techniques for sampling intervillous blood in human beings during labor.[49] Prystowsky[49] has observed a low oxygen tension in the intervillous space and a marked reduction in the maternal-fetal oxygen tension gradient when the infant proved to be in poor condition at birth. The maternal samples were taken just prior to delivery. While the range of oxygen tension in the intervillous sample was wide in the normal group (72 to 26 mm. Hg), in all but three instances, the individual tensions were considerably below a value which would be compatible with an umbilical vein oxygen saturation of 80 per cent. Such findings indicate that, when the head is on the perineum prior to delivery, the various maternal factors tending to lower the fetal oxygenation may already be in action.

Table III and Fig. 4, showing the differences between the cord blood

TABLE IV. COMPARISON OF OXYGEN SATURATION IN UMBILICAL CORD VESSELS

AUTHOR	AVERAGE PER CENT OXYGEN SATURATION		NUMBER OF CASES		RANGE		DELIVERY
	ARTERY	VEIN	ARTERY	VEIN	ARTERY	VEIN	
Eastman[28]	16	50	15	15	6-27	38-58	Vaginal vertex
	30	63	1	1			Caesarean section
Smith[42]	16	51	37	40	2-48	16-81	
Clemetson & Churchman[31]	31	63	10	12	2-50	35-84	Vaginal vertex Spontaneous vaginal vertex
Walker[41]	20	48	9	10	1-28	13-60	Spontaneous vaginal vertex
Rooth & Sjostedt[34]	32	61	69	98	0-62	9-83	Spontaneous vaginal vertex
Present authors (See Table I)	22	49	43	55	0-51	9-85	Cesarean section and vaginal vertex; all vigorous at birth

samples and those obtained from the portal vein, indicate that anoxia causes rapid changes in the pH, Pco_2, and BB. The speed of change as recorded here may be misleading since there was severe cord compression in one infant and one umbilical vein sample has been compared to the two portal vein samples in the case of the twins. However, the rapidity of these changes is well documented in studies on both dogs[8, 9] and adult man.[50] Where the residual air in the lungs has not been washed out with oxygen, the saturation falls to zero in 3 minutes (dogs) and to 28 per cent in 2 minutes (adult man).

The results of the present study emphasize the need for obtaining a sample from within the depressed infant if the limits of respiratory and metabolic acidosis are to be revealed. It is quite possible that these levels may be dangerous enough to cause irreversible cellular damage in the newborn human. If they occur as rapidly as this study suggests and are dangerous, the need for the greatest dispatch in resuscitating an infant with no oxygen reserves is apparent.

Asphyxia in Relation to the Onset of Respiration.—

In vitro and in vivo studies demonstrate that the brain is depressed by oxygen lack,[51, 52] even slight lowering of the oxygen tension depressing the respiratory center.[53] However, through the action of the chemoreceptors which are stimulated by anoxia and continue to function when the oxygen tension has fallen to zero,[6] this depression may be almost completely masked. Under severe anoxia, breathing takes the form of gasps in which the accessory muscles play a major role. The first gasps of the newborn infant are of this type but are soon replaced by quiet and relatively regular diaphragmatic and intercostal breathing following the rapid expansion of the lungs and oxygenation which normally occur within minutes of delivery.[54-56] Although Miller and Behrle[57] have suggested that the chemoreceptor response is poor in the first 24 hours of life, the occurrence of vigorous first breaths under extreme anoxia provides indirect evidence that the chemoreceptors are indeed functioning actively at birth. It is possible that they may be functioning at a higher threshold which was not reached during the induced hypoxia studies of Miller. The direct recording of action potentials from the proximally severed sinus nerve in newborn and fetal animals by Cross and Malcolm[58] is further evidence of activity.

As in the adult, the respiratory center of the infant is acutely sensitive to carbon dioxide[59, 60] and is probably stimulated both directly[61] and indirectly[6] when the Pco_2 rises. The high Pco_2 shown in most vigorous newborns is likely to play a major role in the first gasp if the anoxia is not severe. Finally the low pH, acting through the chemoreceptors,[6] and the flood of sensory impulses crowding in from the skin, the muscles and the joints[62] doubtless constitute important stimuli of the first breaths. These will be augmented by stimuli from the rapidly adapting stretch receptors in the alveoli[63] as the lungs expand.

With progressively severe asphyxia, a point is reached when the respiratory center is finally so depressed that

it is unable to respond.[51] The Pco_2 and pH which previously stimulated the cells now act as depressants. Schmidt has termed this the Reversal. The exact levels of Pco_2 or pH which will depress the center appear to vary depending on the oxygen level, the degree of metabolic acidosis, and the presence or absence of narcotic drugs.[63-65] As for adults, the multiple factor theory of Gray[66] is the most acceptable to interpret the response of the infant respiratory center. All four factors must be considered in each individual case.

Although the infant may take his first breath when there is no measurable oxygen in umbilical artery blood, the presence of oxygen appears to be essential if respiration is to occur in the presence of severe respiratory and metabolic acidosis. This is apparent not only in the vigorous infants (Table I) who have a particularly high Pco_2 or low BB but also in the depressed group. In the latter, spontaneous respiration occurred only after artificial oxygenation of the infant.

When anesthetic or narcotic agents are present in significant amounts, spontaneous respiration is seen only when the asphyxia is mild (Cyclopropane cases, score 8-10, Table I). With high dosage, when drugs are almost wholly responsible for the apnea, the infant frequently makes his first gasp after an interval of 1 to 2 minutes probably as a result of the stimuli arising as the asphyxia increases (infants receiving cyclopropane, score 5-7). These are the infants who appear vigorous, with good tone and heart rate, yet fail to breathe immediately. In other instances in which asphyxia is already severe, a small dose of anesthetic or narcotic will appear to cause profound depression.

SUMMARY AND CONCLUSIONS

1. Some degree of asphyxia, usually of brief duration, occurs as a result of the delivery process and is a normal finding in all births. This may be caused by several factors operating on the fetal and maternal circulations at the time of delivery. Because of these factors, the cord blood obtained following delivery of the infant can rarely, if ever, give a true indication of the normal intrauterine environment.

2. The blood in the umbilical artery represents the blood supplying the fetal tissues, the blood which reaches the head and upper extremities containing on the average only 4 per cent more oxygen. The blood in the umbilical vein will be related more to the placental exchange at or just prior to delivery and may bear little relation to the fetal arterial oxygen level.

3. Vigorous respiration can occur spontaneously in the absence of measurable oxygen in the umbilical artery blood.

4. Asphyxia produces the same biochemical changes in the infant as in the adult—a respiratory acidosis followed by a superimposed metabolic acidosis.

5. The effects of asphyxia, if not too prolonged, acting through the chemoreceptors, are probably responsible for the initial gasps of the infant.

6. Failure to breathe at birth is caused by either depressant drugs or the severity of the respiratory and metabolic acidosis, the result of prolonged asphyxia.

7. The pH, Pco_2, and BB of the newborn infant's blood give a measure of the degree of an anoxic insult. They may change rapidly if he fails to breathe.

8. In evaluating the biochemical status of a depressed infant, a blood sample taken directly from the infant is more representative of his status than is a sample from the umbilical artery.

9. The severe degrees of metabolic and respiratory acidosis seen in depressed infants stress the need for active ventilation and re-oxygenation of these infants immediately after birth.

10. Since inhalation anesthesia administered to the mother will always augment the metabolic depression, regional anesthesia would seem more desirable for delivery of an infant with fetal distress.

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ACID-BASE HOMEOSTASIS OF THE NEWBORN INFANT DURING THE FIRST 24 HOURS OF LIFE

I. M. Weisbrot, M.D.,* L. S. James, M.B.(N.Z.), C. E. Prince, M.D.,** D. A. Holaday, M.D., and V. Apgar, M.D.
New York, N. Y.

THE low CO_2 content and Pco_2 of the blood of newborn infants, as compared with that of adults, have been frequently reported.[1-6] These findings have been the basis for (1) the concept of a persistent metabolic acidosis,[3, 4] (2) a theoretical explanation of the respiratory drive,[5] and (3) speculation concerning the utilization of anaerobic metabolism for energy in the newborn.[3, 4] However, the blood of women during the last trimester of pregnancy also shows diminished CO_2 content and Pco_2.[7-15] The cause of this change is not known; it has been attributed to hyperventilation,[13] and to the effect of progesterone.[14] Total plasma base is reduced by 8 mEq./L.,[10] but plasma organic acids are normal[11] or reduced.[10] It is the purpose of this paper to compare the acid-base balance of newborn infants with that of pregnant women and to discuss the possible significance of this relationship.

MATERIALS AND METHODS

Umbilical arterial bloods were collected from clamped segments of umbilical cord and were taken to represent the status of the infant's systemic arterial blood at the end of parturition. The analyses of these bloods have been presented.[16] Left atrial samples were drawn from newborn infants during the first hour after birth or at the third hour and again at approximately 24 hours, during atrial catheterization via the umbilical vein. It was not technically possible to sample all infants serially. All infants were quiet during the procedure, many of them sleeping. All weighed over 2,500 grams and were born vaginally or by cesarean section of nondiabetic, nontoxemic mothers. Only bloods of infants with an Apgar score[17] of 6 or better were reported. All infants received routine nursery care, which included a feeding of glucose water at about 8 hours of age, and formula or breast feeding between 12 and 24 hours.

Maternal arterial blood samples were drawn at the time of secondary cesarean section of mothers who were not in labor. Sections were performed under regional anesthesia. Demerol, 50 mg., and scopolamine, 0.4 mg., was the usual premedication, given an hour before surgery. No bloods are reported of any mother who was hyperventilating or restless, who had received inhalation anesthesia, or whose face had been covered with a mask prior to sampling.

From the Anesthesiology Service, The Presbyterian Hospital, Sloane Hospital for Women, Babies Hospital, Departments of Anesthesiology, Obstetrics and Gynecology and Pediatrics, Columbia University, College of Physicians and Surgeons, New York 32, New York.

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*Edan Ros and Public Health Research Fellow.

**Macy Foundation Fellow.

Bloods were collected anaerobically in greased syringes, the deadspaces of which were filled with a concentrated heparin solution. They were rotated through ice water until analyzed. Oxygen saturation, pH, carbon dioxide content, and hematocrit were determined by methods previously described.[16] The pH of atrial blood specimens was measured at 37° C. and was corrected to deep rectal (6-7 cm.) temperature, according to the formula of Rosenthal.[18] The P_{CO_2} was calculated from the Henderson-Hasselbalch equation, using pK′ and solubility coefficient of CO_2 corrected to the infant's body temperature according to the values of Severinghaus and his associates.[19, 20] The P_{CO_2} of the other bloods and the buffer base (BB) was determined from the Singer and Hastings nomogram.[21]

RESULTS

The results of the blood gas analyses are shown in Tables I-V. The mean values for 12 maternal samples (Table I) were pH—7.39; plasma CO_2 content—19.96 mEq./L.; P_{CO_2}—31.7 mm. Hg; and BB—41.8 mEq./L. of whole blood. Despite our maternal control subjects not having been in a basal state, our value for P_{CO_2} was in good agreement with the alveolar P_{CO_2} tension determinations of other authors, which are tabulated below.

Author	*P_{CO_2}, mm. Hg*
Rowes	29.9 and 30.9
Goodland et al.[14]	30 (approximately)
H. and E. Bouterline-Young[15]	30.9
Present study	31.7

Our value for arterial plasma CO_2 content was somewhat lower than the venous plasma values of other authors, which are tabulated below.

Author	*Plasma CO_2, mEq./L.*
Dennis and King[9]	23.1 (venous)
Oard and Peters[10]	22.1 (venous)
Stander et al.[11]	21.8 (venous)
Muntwyler et al.[12]	22.7 (venous)
Present study	19.96 (arterial)

Our value for pH was within the normal adult range and confirms the findings of Kydd.[22]

The data of Tables II-VI indicate that the infant is subjected to a period of anoxia, CO_2 retention, and acidosis during parturition which recede rapidly after birth. At 24 hours of age

TABLE I. ACID-BASE BALANCE OF 12 PREGNANT WOMEN AT TERM
ARTERIAL SAMPLES

	OXYGEN SATURATION (PER CENT)	pH BLOOD	P_{CO_2} MM. HG	CO_2 CONTENT MEQ./L. PLASMA	BUFFER BASE MEQ./L. BLOOD
Dov	95.1	7.38	35	21.3	42.0
Rod	95.0	7.44	28	19.2	42.2
Jac	96.6	7.37	30	18.0	40.2
Ric	96.4	7.42	31	20.1	42.3
Fol	93.7	7.34	35	19.5	40.2
Han	93.4	7.39	32	19.5	40.8
Burn	95.1	7.31	33	17.3	37.4
Ben	96.5	7.47	33	24.4	47.2
Mag	93.6	7.39	33	20.3	41.3
Burk	97.6	7.42	26	17.4	43.0
Lev	95.0	7.41	30	19.9	42.0
Men	94.0	7.39	35	22.6	43.5
Average	95.17	7.393	31.7	19.96	41.84
S.D.	1.36	0.043	2.8	2.08	2.23

TABLE II. ACID-BASE BALANCE DURING BIRTH OF 21 INFANTS
UMBILICAL ARTERY SAMPLES

	TYPE OF DELIVERY	OXYGEN SATURATION (PER CENT)	pH BLOOD	P_{CO_2} MM. HG	CO_2 CONTENT MEQ./L. PLASMA	BUFFER BASE MEQ./L. BLOOD
Lob	Vaginal	0.0	7.32	44	20.5	41.5
Tor	Vaginal	9.2	7.28	46	22.3	39.6
Dov	Cesarean	0.0	7.23	64	26.5	41.4
Vel	Vaginal	7.0	7.12	64	21.6	33.7
Aie	Cesarean	8.2	7.22	64	27.0	41.7
Lor	Cesarean	23.9	7.27	53	25.5	42.1
Dod	Cesarean	30.9	7.30	50	25.7	43.0
Cha	Cesarean	47.8	7.26	49	23.8	40.9
Jac	Cesarean	30.1	7.28	—	—	—
Rod	Cesarean	30.9	7.30	43	22.5	44.8
Pie	Vaginal	17.2	7.20	63	26.2	40.5
Hal	Vaginal	30.5	7.15	64	23.7	37.1
Bea	Cesarean	4.0	7.20	67	28.3	41.3
Mag	Cesarean	21.1	7.22	54	23.3	39.3
Sch	Cesarean	7.0	7.10	64	21.4	33.7
Mel	Vaginal	9.4	7.23	53	23.2	38.4
Burk	Cesarean	28.1	7.27	50	24.3	41.2
Men	Cesarean	39.5	7.30	54	28.3	44.8
Mon	Vaginal	2.2	7.20	62	25.6	39.2
Rei	Vaginal	0.0	7.18	59	23.5	37.0
Gib	Vaginal	10.5	7.22	92	38.6	51.7
	Average	17.02	7.231	58.4	25.04	40.65
	S.D.	14.41	0.062	10.5	3.89	3.98

TABLE III. ACID-BASE BALANCE DURING FIRST HOUR OF 10 INFANTS
LEFT ATRIAL SAMPLES

	TYPE OF DELIVERY	OXYGEN SATURATION (PER CENT)	pH BLOOD	P_{CO_2} MM. HG	CO_2 CONTENT MEQ./L. PLASMA	BUFFER BASE MEQ./L. BLOOD
Woo	Vaginal	93.8	7.31	37	21.3	42.0
Jac	Cesarean	91.7	7.43	28	20.4	44.8
Ric	Cesarean	88.1	7.22	51	22.8	40.5
Burn	Vaginal	94.9	7.22	48	21.2	40.3
Tho	Vaginal	97.4	7.30	42	21.7	42.8
Hal	Vaginal	93.2	7.26	38	18.6	39.5
Bea	Cesarean	94.0	7.35	41	24.3	46.8
Mag	Cesarean	96.0	7.25	34	16.2	37.5
Mel	Vaginal	94.0	7.29	38	19.5	41.1
Del	Vaginal	95.2	7.41	31	20.2	46.4
	Average	93.83	7.304	38.8	20.62	42.17
	S.D.	2.55	0.023	7.3	2.27	3.39

TABLE IV. ACID-BASE BALANCE AT THIRD HOUR OF 7 INFANTS
LEFT ATRIAL SAMPLES

	TYPE OF DELIVERY	OXYGEN SATURATION (PER CENT)	pH BLOOD	P_{CO_2} MM. HG	CO_2 CONTENT MEQ./L. PLASMA	BUFFER BASE MEQ./L. BLOOD
Han	Cesarean	98.0	7.29	46	22.5	41.9
Pie	Vaginal	94.4	7.37	36	22.6	46.3
Wal	Cesarean	95.1	7.35	39	23.4	44.8
Burk	Cesarean	95.1	7.31	39	21.3	42.4
Duc	Vaginal	94.4	7.35	41	22.9	45.2
Per	Vaginal	93.2	7.37	32	19.2	43.8
Fly	Vaginal	92.6	7.35	35	21.2	43.2
	Average	94.69	7.341	38.3	21.87	43.94
	S.D.	1.73	0.030	6.1	1.42	1.58

TABLE V. ACID-BASE BALANCE AT 24 HOURS OF 14 INFANTS
LEFT ATRIAL SAMPLES

	TYPE OF DELIVERY	OXYGEN SATURATION (PER CENT)	pH BLOOD	P_{CO_2} MM. HG	CO_2 CONTENT MEQ./L. PLASMA	BUFFER BASE MEQ./L. BLOOD
Burn	Vaginal	92.2	7.35	37	21.1	42.8
Pie	Vaginal	91.7	7.36	39	23.5	45.3
Tho	Vaginal	93.1	7.37	35	21.4	43.8
Mag	Cesarean	98.0	7.39	35	21.7	43.2
Del	Vaginal	96.6	7.42	31	21.1	46.9
Lop	Vaginal	98.0	7.42	31	20.5	46.5
Sil	Vaginal	92.0	7.40	28	18.2	43.5
Bir	Vaginal	86.4	7.48	30	22.5	46.4
Cro	Vaginal	97.5	7.42	33	21.9	46.5
Reu	Cesarean	86.9	7.49	37	20.5	44.5
Sto	Cesarean	97.2	7.41	33	21.8	44.2
Gav	Cesarean	91.9	7.40	37	24.0	47.6
Fly	Vaginal	91.0	7.40	35	22.7	44.9
Bar	Vaginal	92.2	7.41	29	18.6	40.3
	Average	93.19	7.408	33.6	21.38	44.74
	S.D.	3.85	0.039	3.4	1.63	1.98

TABLE VI. STATISTICAL COMPARISON OF INFANT BLOOD VALUES AT EACH TIME WITH MATERNAL CONTROLS*

	pH	p	P_{CO_2}	p	CO_2 CONTENT	p	BUFFER BASE	p
Birth (Umb. A.)	7.23	$<.01$	58.4	$<.01$	25.04	$<.01$	40.7	$>.10$
During first hour	7.30	$<.01$	38.8	$<.02$	20.62	$>.10$	42.2	$>.50$
At third hour	7.34	$<.01$	38.3	$<.01$	21.87	$<.05$	43.9	$<.05$
At 24 hours	7.41	$>.10$	33.6	$>.10$	21.38	$>.05$	44.7	$<.01$
Maternal	7.39		31.7		19.96		41.8	

*p values less than 0.05 are taken to represent statistically significant differences between maternal and infant values.

there is no statistical difference between the means of maternal and infant pH, P_{CO_2}, and CO_2 content. The newborn child would seem to move toward the level of pH and P_{CO_2} to which he was exposed in utero.

Fig. 1 is a plot of the pH and CO_2 content data taken from Tables I-V, showing the changes which occur through time with respect to our maternal control values and to normal adult values as given by Peters and Van Slyke.[23]

In Fig. 2 the results obtained by Graham and Wilson[5] from heel capillary blood of 24-hour-old infants is presented. In this method, blood is obtained by pricking the heel and collecting the blood under mineral oil. The ensuing crying of the infant and the possible loss of CO_2 into the mineral oil may cause variation from basal arterial values. The results of Marples and Lippard[2] for *venous* blood of 1- to 8-day-old infants are shown in Fig. 3. (Comparable *arterial* blood of these infants could be expected to contain 1.5 to 2 mEq./L. less CO_2, bringing these data even closer to the range of maternal control values.) The results of these laboratories tend to confirm our finding that although newborn infants have a CO_2 deficit with respect to normal adults, no such deficit exists with respect to pregnant women near term.

Buffer base rises steadily from birth to a mean level of 44.7 mEq./L. of whole blood at age 24 hours, a value

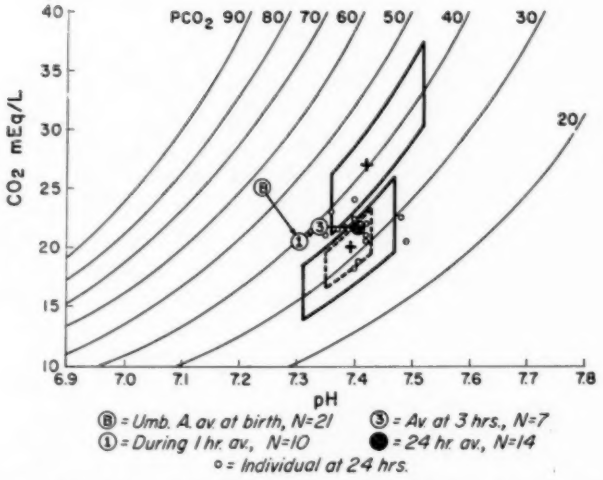

Fig. 1.—The ordinate is mEq./L. plasma CO_2. The abscissa is pH. The curved lines are P_{CO_2} isobars and are logarithmically spaced. The upper quadrilateral represents the range of normal adult arterial values. The lower quadrilateral represents the range of maternal arterial values, with one S.D. from the mean indicated by broken lines.

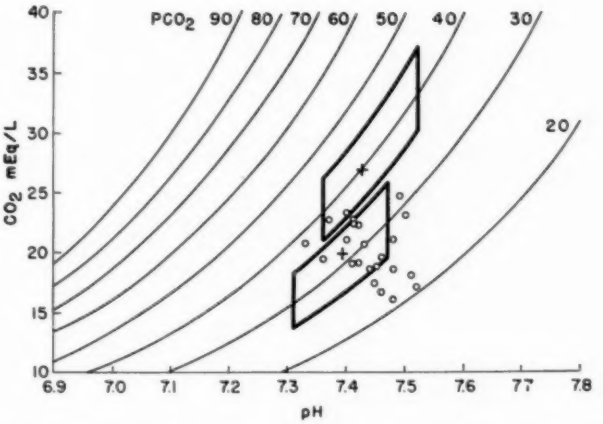

Fig. 2.—Capillary (arterial) blood—24 hours of age. Data of Graham and Wilson[5] plotted in open circles. The quadrilaterals represent normal arterial values and data from pregnant women, respectively, as in Fig. 1.

which is higher than the maternal level but lower than the mean normal adult value of 49 mEq./L.[21]

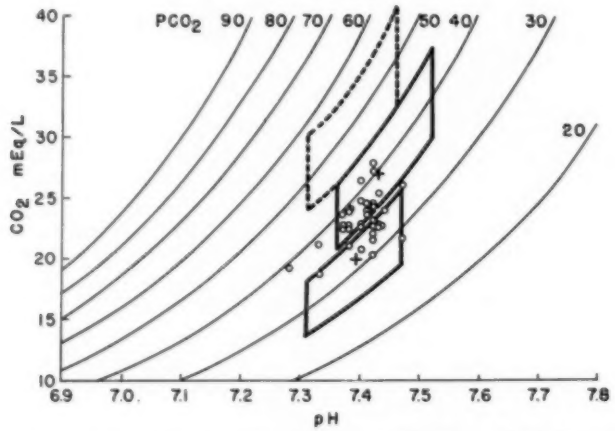

Fig. 3.—Venous blood—ages 1-8 days. Data of Marples and Lippard[2] plotted as open circles. Upper quadrilateral, outlined by dashed lines, includes additional range of adult normal venous blood. Lower quadrilaterals are as for Figs. 1 and 2.

DISCUSSION

From the data of Tables I-VI and Fig. 1, it appears that after the stress of parturition the homeostatic mechanisms of the newborn are directed toward attaining a pH and Pco_2 which existed in utero. In reviewing the early work attempting to establish the relation between maternal and fetal CO_2 tension, Bareroft[24] concludes that only a small difference should be expected. Barron,[25] in careful experiments on sheep, has shown that the alkali reserve of the ewe and that of its near-term fetus are almost identical.

Previous attempts to explain the low Pco_2 and CO_2 content of the blood of newborn infants dealt chiefly with two hypotheses, as follows: (1) the possibility that hyperventilation due to anoxia caused lowering of Pco_2 and (2) the possibility that anaerobic metabolism caused lessened CO_2 production and accumulation of intermediary organic acids leading to a metabolic acidosis.

Hyperventilation Due to Anoxia Hypothesis.—Graham and Wilson[5] have explained the low Pco_2 of babies at 24 hours of age as the result of hyperventilation due to anoxic stimulation of the aortic and carotid chemoreceptors. During the first hour of life, they noted oxygen saturation of capillary blood from the heel to the level of 85 per cent, corresponding to an O_2 tension of 50 mm. Hg. They do not state whether the heel was arterialized by warming prior to sampling. Persistent cyanosis of the feet is common in healthy infants during the first day and probably represents local circulatory stasis rather than systemic arterial desaturation. Left atrial saturations during the first day are given in Tables III-V. The saturation is about 94 per cent during the first hour and does not change appreciably with time. These results confirm our suspicion that heel capillary blood may not represent true arterial samples.

We may assume that the respiratory center of the fetus in utero adapts to the low P_{CO_2} environment supplied by its mother and that the rise in P_{CO_2} during parturition supplies one of the chemical drives to respiration, subsequently. It is known in animals that experimental elevation of maternal P_{CO_2} will cause respiratory movements of the fetus in utero.[26]

The exact nature of the hypoxic chemoreceptor drive to respiration in newborn infants is not clear. Cross and Warner[27] have demonstrated a small rise in minute volume during the first week of life in infants exposed to an atmosphere of 15 per cent O_2, while Miller and Behrle[28] have not recorded such a rise in infants, one day old or less, given 12 per cent O_2 (approximate alveolar P_{O_2} of 50 mm. Hg). Thus, the level of arterial P_{O_2} at which Graham and Wilson postulate a strong hypoxic stimulus may not actually produce one. Moreover, the recent work of James and Rowe[29] indicates that very low oxygen tensions cause profound circulatory changes which further decrease systemic arterial saturation. However, both Cross[30] and Miller[31] agree that CO_2 is a potent stimulus to respiration. We postulate that the low P_{CO_2} of the newborn at 24 hours represents the end results of the respiratory center's efforts to attain a level of P_{CO_2} similar to that to which it had been exposed in utero.

Anaerobic Metabolism With Production of Organic Acids and Metabolic Acidosis Hypothesis.—Wilson and his associates[3] postulated that anaerobic metabolism, with diminished CO_2 production, accounted for the low plasma CO_2 content of newborn infants. They cited the prolonged survival time of newborn laboratory animals made severely anoxic as additional proof of the role of anaerobic metabolism in young animals. However, the ability of young laboratory animals to survive anoxic stress is not necessarily proof of increased capacity for anaerobic metabolism over that of the adult. Villee and Kimmelstiel[32] have calculated that anaerobic glycolysis will probably not provide sufficient energy to explain survival in these animals. Moreover, in clinical obstetrics, the infant can withstand only a few minutes of anoxia such as might occur during impaction of the shoulders.

Graham and co-workers[4] have shown the plasma "R" fraction (which consists largely of organic acids) to be 15 mEq./L. for 24-hour-old infants, whereas that of the adult is only 10 mEq./L. Räihä,[33] in discussing fetal tissue metabolism, states, "The acidosis demonstrated in the newborn is largely due to organic acids, chiefly to pyruvic and lactic acids. . . ." The blood pyruvate level he observed was 1.18 mg. per cent or 0.52 mg. per cent above adult levels. Gonzales and Gardner[34] have shown a similar difference in pyruvate level between infants during the first 24 hours of life and pregnant women. Such a difference would contribute about 0.1 mEq./L. of plasma to the excess "R" value. Blood lactate levels in somewhat older infants were found by Brehme[35] to be 8 mg. per cent above adult levels, which would contribute only about 1.2 mEq./L. of plasma to the "R" value. Thus, the products of anaerobic glycolysis account for only one quarter of the excess "R" value. Leopold and Bernhard[36] found no relation between lactate level and CO_2 combining power in older children.

The data of Tables II-V indicate that buffer base rises steadily after birth, but that at 24 hours it is still below the normal adult level of 49 mEq./L. (though higher than the maternal level). Reduction of buffer base means, by definition, metabolic acidosis. However, it is not necessary to assume that this acidosis is a result of increased capacity of the fetus and newborn for anaerobic glycolysis. Holaday and associates[37] have demonstrated in anesthetized man and animals that CO_2 retention is capable of producing a prolonged fall in buffer base by a mechanism yet to be elucidated. The work of Singer and his colleagues, quoted by Dripps and Severinghaus,[38] indicates the possibility of migration of hydrogen ion from the cell to the extracellular fluid during CO_2 retention. It is possible that CO_2 retention during parturition induces a similar change in the human infant. Further investigation of the acid-base balance of the fetus in utero is necessary to answer this question.

SUMMARY AND CONCLUSIONS

In evaluating the significance of the low Pco_2 and CO_2 content in the blood and plasma of newborn infants, consideration should be given to the fact that this state also exists in the pregnant woman during the last trimester. Interpretations of the status of the newborn infant's respiratory drives and acid-base metabolism made with respect to normal adult values may be misleading.

Grateful acknowledgment is made to our technicians, Miss Iris Weiss, Miss Mariagnes Verosky, Mrs. Jean Mac Lachlan, Mrs. Ann Shustak and Mr. Wallace Luke for their excellent chemical determinations, and to the obstetrical nursing staff headed by Miss D. Robinson, the newborn nursery nursing staff headed by Miss S. Schneider, and to our nurse, Mrs. Peggy S. Rotton, without whose generous assistance this work could not have been done.

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REACTION OF 150 INFANTS TO COLD FORMULAS

JOHN P. GIBSON, M.D.
ABILENE, TEXAS

THE young mother asked, "Will cold milk hurt my baby? I gave him an ice-cold formula the other night. I was so tired I didn't realize what I was doing, but he liked the milk cold and now prefers all his bottles straight out of the refrigerator. Will it hurt him?"

The baby, 6 weeks old, seemed perfectly healthy and happy, so what was the answer to her question? After this same inquiry came from several other mothers following similar incidents, I began to ask questions. I soon found that quite a few mothers had stumbled into this same practice of giving cold formulas, and that a surprising number of infants were being given ice cream, all with obvious enjoyment, and none with any apparent harmful results.

Questions presented themselves for further study:

1. Is the practice of warming formulas based upon necessity or tradition?

2. What is the acceptance rate on the part of young infants to cold formulas?

3. Do cold formulas have any harmful effect on the babies?

Information on these points would be important to mothers who prepare about 1,400 bottles of formula during the first 8 months of the baby's life. Do they need to warm all those bottles? This question becomes still more urgent in the middle of the night and on trips. It is of importance to us as physicians to know whether cold formulas are harmful to infants.

METHODS

Since no studies could be found in medical literature dealing with the problem of giving cold formulas to infants, I began with my own patients in private practice. As the mothers would bring their babies to the office for their regular monthly examinations I would ask, "Mother, wouldn't it be nice if you didn't have to warm all those bottles?" She would respond, "Oh, that would be wonderful! Tell me more." I would then suggest that if she would warm each bottle a little less each time, before long the baby might prefer his bottle either cool or straight out of the refrigerator. No time schedule was suggested and bottle temperatures were not taken. The enthusiasim with which the mothers acted on this suggestion was remarkable.

At the monthly visits, the infants were weighed, measured, and given a complete examination, and the mother reported on her experiences. The mothers described a cool formula as one that had been removed from the refrigerator and allowed to stand in the kitchen "until the chill was off" or "until it approached room temperature." A cold bottle was one taken

directly from the refrigerator and given to the baby. Usual temperatures of formulas from refrigerators are about 40° F. or 5° C. All of the babies were changed gradually from warm to cool to cold bottles.

There are 150 infants in my private practice who have been offered cold formulas. Of these, 69 are males, 81 females. All are white except for 1 Negro and 1 Mexican. Their ages range from 15 hours to 7 months.

convinced that the cold formulas had "cured the colic" for their babies. In the other 9 there was apparently no change. In 3 other babies, not in this group, the mothers felt that the cold formulas had caused the babies to have "gas pains," so no further effort was made to give them cold bottles. This group is too small to be of significance.

In assessing the developmental progress of the 134 infants who accepted cool and cold formulas, a complete ex-

ACCEPTANCE RATE

TABLE I. ACCEPTANCE OF COOL AND COLD FORMULAS BY 150 INFANTS

AGE GROUP	NUMBER	REFUSED COOL OR COLD MILK	ACCEPTED COOL MILK	ACCEPTED COLD MILK	AVERAGE INTERVAL FOR CHANGE (DAYS)
1 day to 3 weeks	43	3	17	23	7
1 to 3 months	68	6	20	42	6
3½ to 7 months	39	7	4	28	7
Totals	150	16	41	93	average 6-7

TABLE II. SUMMARY OF WEIGHT CURVES OF 120 INFANTS CHANGED TO COOL OR COLD FORMULAS, AND FOLLOWED FOR AN AVERAGE OF 6.7 MONTHS AFTER THE CHANGE

AGE GROUP	CONSISTENT WEIGHT CURVES				WEIGHT CURVE DEVIATIONS	
	NUMBER	ABOVE AVERAGE	AVERAGE	BELOW AVERAGE	UPWARD	DOWNWARD
1 day to 3 weeks	38	18	15	1	4	0
1 to 3 months	56	34	16	3	3	0
3½ to 7 months	26	16	8	2	0	0
Totals	120	68	39	6	7	0

It was noted that the acceptance rate for cold formulas varied from about 50 per cent (23 of 43) for the very young infants to about 75 per cent (28 of 39) in the older group. For the whole group of 150, the acceptance rate for cool or cold formulas was 89 per cent, within an average period of one week.

EFFECT OF UNHEATED FORMULAS ON INFANTS

There were 11 infants in the group who could be classified as "gassy" or "colicky." Two of the mothers were

amination was made each month. Weight records were plotted on a chart with the average curve starting at 7½ pounds, curving up to 14 pounds at 5 months, and 20 pounds at 12 months. More attention was given to a consistent weight curve parallel to the average than to actual poundage. Weight curves were classified as: (a) consistently above average, both before and after the change to unheated formulas; or (b) consistently average, before and after the change; or (c) consistently below average, before and after the change.

All of these curves were considered satisfactory, if consistent, and if the infant's general condition was good. Search was made for deviations in the weight curve either upward or downward that coincided with or followed a change to unheated formulas.

All of the weight curves were consistent before and after the change to unheated formulas, except for 7 infants who had a marked deviation upward in their weight curves coinciding with the change. No infant had a downward deviation.

EFFECT ON BODY TEMPERATURE

One mother who had just been delivered of her second baby requested, "Please train my baby to take his formula cold while he is in the nursery; my first child did so well on cold formulas." This presented an opportunity to record body temperatures after taking a cold formula. The infant (6 pounds, 11 ounces) had received one warm bottle when he was 12 hours old, taking it well. At the age of 15 hours, rectal temperature was taken and an ice-cold formula offered, which he also took well (about 2 ounces). Rectal temperatures were then taken immediately after feeding, and at intervals of 5, 10, and 30 minutes later. This was repeated for the next 8 cold formulas, average 1½ to 2 ounces each. In the 25 postformula temperatures there was no reduction of temperature in 12; a reduction of 0.2 degree in 6, a reduction of 0.4 degree in 1, and a reduction of 0.6 degree in 2, a reduction of 0.8 degree in 2, and an elevation of 0.2 degree in 1.

This infant started to gain weight on the second day. At the age of 13 days, the weight was 7 pounds, and at 1 month it was 8 pounds, 10 ounces, with general condition excellent.

CONCLUSIONS

1. In a group of 150 infants, cool or cold formulas were accepted by 89 per cent.

2. In 120 of the infants accepting cool or cold formulas and followed for an average of 6.7 months, development proceeded normally.

3. No harmful effects could be found in the infants accepting the cool and cold formulas.

THE MYELOPROLIFERATIVE SYNDROME IN CHILDREN

HARVEY S. ROSENBERG AND FRED M. TAYLOR
HOUSTON, TEXAS

FIBROSIS of the bone marrow with extramedullary hematopoiesis is occasionally associated with certain hematologic disorders including polycythemia vera, agnogenic myeloid metaplasia, and erythroleukemia. It has been proposed that these anatomic changes represent a syndrome of chronic demand upon hematopoiesis resulting in "en masse" proliferation of bone marrow.[1]

The following synonyms emphasize the striking number of pathologic interpretations applied to this syndrome: (1) subacute myelosclerosis, (2) leukoerythroblastic anemia, (3) osteosclerosis, (4) chronic nonleukemic myelosis, (5) osteosclerotic myelopathy, (6) aleukemic myelosis, (7) agnogenic myeloid metaplasia, and (8) erythroleukemia.

There is no relationship with the osteosclerotic process of Albers-Schonberg, in which there is excess calcification of bony cortex, absence of bone lamellae, defective ossification, and absence of osteoblastic activity. This contrasts with primary myelofibrosis where the marrow is obliterated by fibrous or bony tissue and the cortex is spared with little or no effect.[2]

Disorders in myeloproliferation are usually described in older age groups. Less than a dozen instances of this disease have been identified and reported in pediatric subjects. The purpose of this paper is to report the finding of myelofibrosis in 2 children, and to review and discuss the literature concerning this disorder.

From the Departments of Pathology and Pediatrics, the Texas Children's Hospital and Baylor University College of Medicine, Houston, Texas.

CASE REPORTS

CASE 1.—A 23-month-old white female infant with mongolism was hospitalized in Texas Children's Hospital because of anemia for three months and a respiratory infection for one month which had not responded to treatment with iron-cobalt mixture, penicillin, and streptomycin.

The mother was 26 years of age. Pregnancy, labor, and delivery had not been complicated. Mongolism was recognized shortly after birth. Subsequent motor and mental development was slow. The diet was limited principally to milk and cereal. There were no previous illnesses and no previous medications. Immunization included a single inoculation of diphtheria-pertussis-tetanus.

By physical examination, pallor was conspicuous. The liver extended 2.0 cm. and the spleen 3.0 cm. below the respective costal margins. Hemoglobin was 4.4 Gm./100 c.c. The red blood cell count was 1,270,000, and the white blood cell count 5,400. The differential count contained 1 blast cell, 5 promyelocytes, 12 myelocytes, 24 metamyelocytes, 12 polymorphonuclear cells, 3 monocytes, and 43 lymphocytes. The reticulocyte count was 0.5 per cent. After a whole blood transfusion, the hemoglobin rose to 8.0 Gm./100 c.c., and she was discharged.

She was readmitted three weeks later because of episodes of fever lasting 12 to 24 hours. Fever was refractory to therapy during the week before rehospitalization.

The physical examination was unchanged. Hemoglobin was 6.7 Gm./100 c.c. The red blood cell count was 2,400,000 and white blood cell count 23,450. About 60 per cent of the white

blood cells were identified as blast cells. Red cells were hypochromic. Capillary bleeding time was 2 minutes, 20 seconds and the capillary clotting time was 4 minutes, 45 seconds. The platelet count was 117,000 and the clot retraction was normal. The serum bilirubin was 0.3 mg./100 ml. Febrile agglutinations were negative. The heterophile antibody was positive 1:7. Urinalysis was normal. The serum VDRL was negative. Two bone marrow aspirations were so completely made up of peripheral blood that they were unsatisfactory for diagnosis. A diagnosis of acute leukemia was made on the basis of the findings in the peripheral blood film.

She was given a blood transfusion and cortisone, 200 mg. daily. Cortisone was decreased to 75 mg. daily after four days. Irritability and somnolence increased. Hemoglobin dropped to 4.8 Gm./100 ml. but rose to 10.3 Gm./100 ml. after blood transfusion. The white blood cell count was now 200,000.

The final hospitalization was two weeks later, because of persistent fever, paroxysmal coughing, and small ulcers in the mouth. Hemoglobin was 12.6 Gm./100 ml. The white blood cell count was 9,600 and all cells were described as blasts. *Pseudomonas aeruginosa* was cultured from the blood and pharynx. She died two days after admission.

Autopsy Report.—The physical features of mongolism were present.

The right and left lungs weighed 160 and 100 Gm., respectively. An area of firm consolidation containing multiple firm, red-gray nodules was found in the dependent portions of each lung. Each pleural space contained about 75 ml. of cloudy yellow fluid and a few thin, friable adhesions.

The spleen weighed 310 Gm. in contrast to an average of 33 Gm. for this age. The capsule was purple-gray and intact. The cut surface was fleshy and fibrotic with a semitranslucence of the trabecular structure. Lymphoid follicles were not apparent grossly. The marrow space of a rib was homogeneously pale yellow and contained no visible normal marrow. The lymph nodes were enlarged but discrete, and their cut surfaces were homogeneous without obvious change from normal. The liver weighed 570 Gm. in contrast to an average of 394 Gm. The lobular architecture was prominent.

There was a chronic gingivostomatitis. Multiple petechiae were present in the mucosa of the stomach, small intestine, and colon.

A Pseudomonas of unidentified species was cultured from the lung and the heart's blood.

Microscopically, there was extensive pulmonary edema with numerous deposits of fibrin in which clumps of bacteria were present. Focal areas of complete necrosis of the lung were associated with a striking paucity of acute inflammatory cells. Many large mononuclear cells and a few large bizarre multinucleated forms were present.

The red pulp of the spleen was filled with a remarkably pleomorphic cell population (Fig. 1). The most conspicuous cell was large and irregular with both multinucleated and multilobed nucleus forms. In both types, the nuclei were deeply basophilic and rarely contained nucleoli, and the cytoplasm was deeply eosinophilic and finely granular. Many immature granulocytes were present. A few small foci of erythropoiesis were present. Several small lymphoid follicles were present and, in some areas, remnants of a follicle which had been replaced by myeloid elements could be identified. Deposits of collagen in a loose fibrillar pattern about the lymphoid follicles were identified in the Mallory's aniline blue stain. In addition, the reticulum structure was accentuated throughout the spleen. Nests of large, bizarre cells in groups of three or four were surrounded by a prominent reticulum band. A moderate quantity of iron was identified by the Gömöri's iron stain.

A few of the large cell types were seen within the sinusoids of the liver. The architecture of the liver was well preserved, however, and there was no cellular infiltration.

Fig. 1.

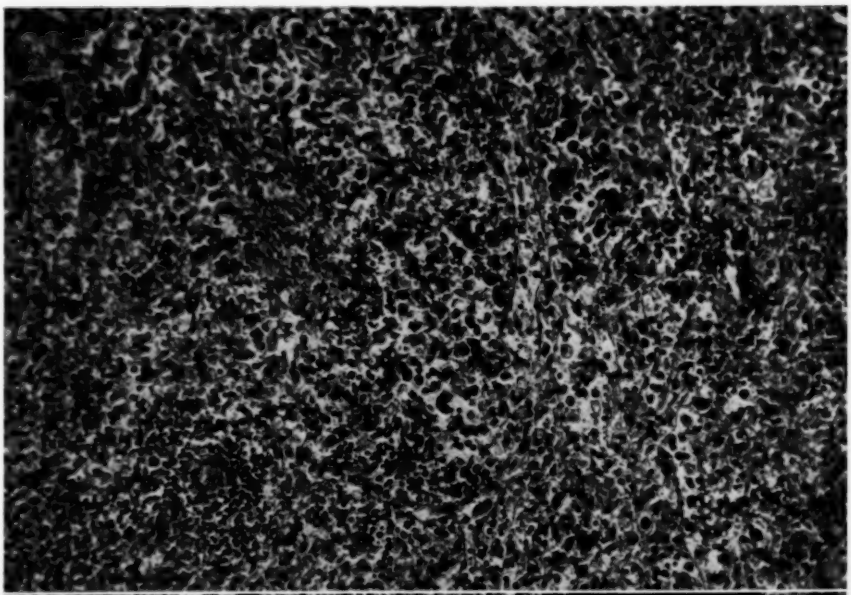

Fig. 2.

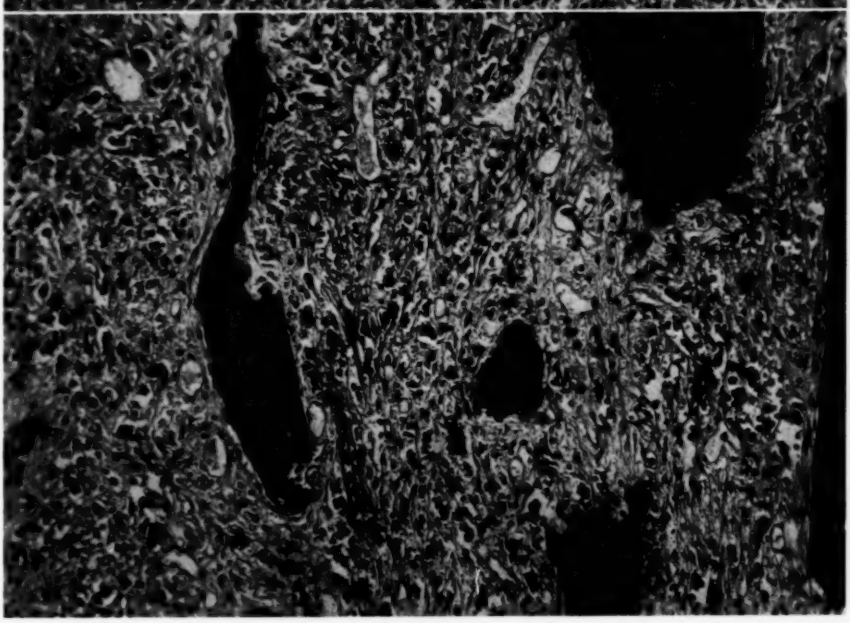

Fig. 1.—In the spleen of Case 1 there is a prominent myeloid metaplasia with many megakaryocytes. A depleted lymphoid follicle is present.

Fig. 2.—In the marrow of the rib of Case 1 there is a paucity of cells associated with a thickening of reticulum and many megakaryocytes.

The supraclavicular lymph nodes were distorted by extensive hemorrhage and, in addition, contained large colonies of bacteria. A few large multinucleated cells were also present within the substance of the node. Reticulum cells were prominent in the mediastinal and mesenteric nodes. Lymphatic vessels were dilated and filled with mononuclear and a few multinucleated cells, although the stroma showed marked lymphoid depletion. A mediastinal node contained an area of necrosis associated with bacterial colonies.

There was a general replacement of bone marrow substance by a marked degree of fibrosis (Fig. 2). Trabeculae were diminished considerably in number and size. There was little change in the cortical bone. Proliferation of reticulum and increase of collagen content were identified in this area. No free iron was found. A few islands of cellularity consisted solely of clumps of poorly differentiated mononuclear and large multinucleated cells.

A single, small, subcortical hemorrhage was present in the cerebral cortex with no associated cellular response.

CASE 2.—A 13-month-old white female infant was hospitalized because of anemia. She had had repeated episodes of otitis media requiring several myringotomies. The mother had had a splenectomy at 12 years of age because of "Banti's disease," and had since received iron medication.

The patient was pale but otherwise vigorous. The spleen was palpable 5.0 cm. below the left and the liver 3.0 cm. below the right costal margin.

Hemoglobin was 5.9 Gm./100 ml. and the red blood cell count was 3,240,000. Urinalysis was negative. The VDRL was negative. The capillary bleeding time was 3 minutes, 45 seconds. Clotting time (capillary) was 4 minutes, 20 seconds. Osmotic fragility of the red cells was the same as the control. A bone marrow aspiration was diluted with peripheral blood and was not diagnostic. She was discharged from the hospital and readmitted three weeks later. Physical examination disclosed no change.

Hemoglobin was 11.3 Gm./100 ml. Prothrombin concentration was 100 per cent of normal. Serum bilirubin was 0.5 mg./100 ml. Total serum protein was 7.4 Gm./100 ml. with 5.0 Gm. of albumin and 2.4 Gm. of globulin. Thymol turbidity was 5.8 units. The fasting blood sugar was 80.0 mg. and blood urea nitrogen 12.0 mg./100 ml. Roentgenograms showed normal esophagus, skull, knees, and pelvis. A bone marrow biopsy showed moderate, generalized hyperplasia with a few small lymphoid follicles (Fig. 3). She was discharged 4 days later.

During the following seven months she was hospitalized twice because of steady fall in the hemoglobin level. She was treated with whole blood transfusions each time. At the end of this time, she was hospitalized for splenectomy. Hemoglobin was 14.5 Gm./100 ml. White blood cell count was 13,750. Splenectomy and liver biopsy were performed under general anesthesia. The surgical specimen included congestive splenomegaly (Fig. 4), a single accessory spleen, and a hyperplastic lymph node. No abnormality was found in the liver. Four days after operation, she had fever of 104° F. and erythema and edema of the mucous membranes of the mouth and gums. White blood count was 7,200 with 31 per cent segmented neutrophils, 12 per cent band forms, 51 per cent lymphocytes, 2 per cent monocytes, and 4 per cent eosinophils. The following day a confluent rash was present on the entire body. Suboccipital lymphadenopathy was noted also, and a diagnosis of rubella was made. By the seventh hospital day, however, fever was still present and generalized lymphadenopathy was present. The skin rash disappeared the following day, lymphadenopathy

Fig. 3.

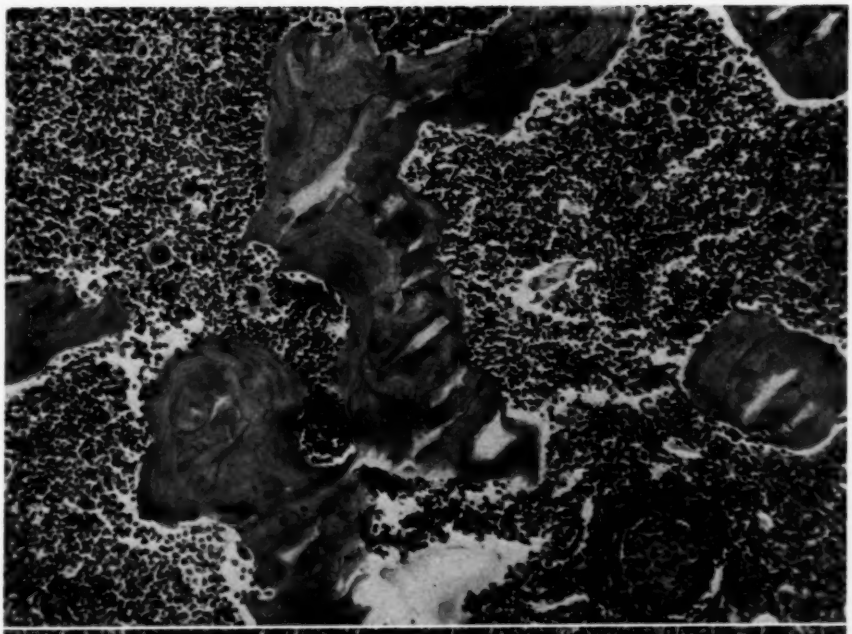

Fig. 4.

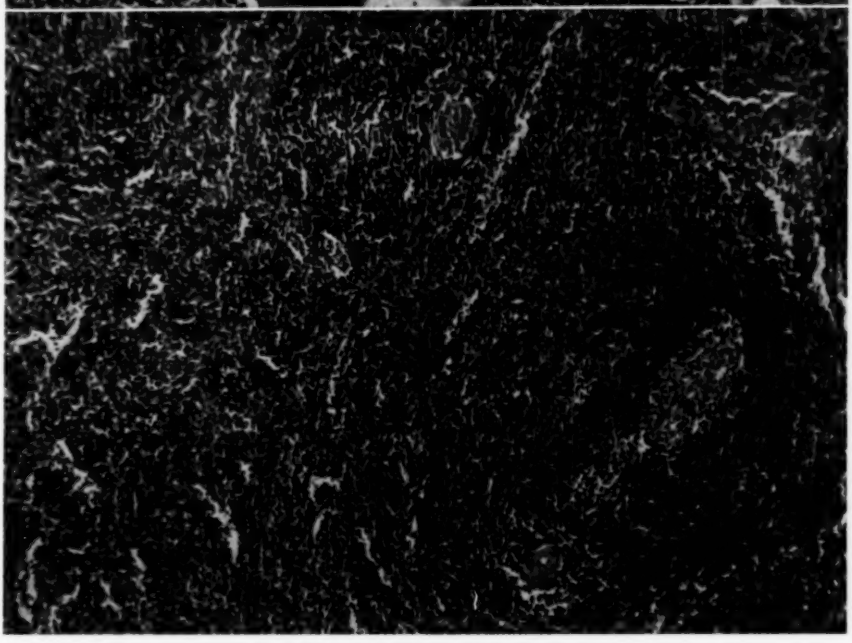

Fig. 3.—The surgical bone biopsy of Case 2 contains a cellular marrow whose structure is marred only by the presence of a single lymphoid follicle.

Fig. 4.—In the surgically excised spleen of Case 2 there is a moderate fibrosis of the red pulp associated with a normal pattern of lymphoid follicles.

was the same, but her general condition was such that she was discharged for home care.

During the next three days new skin lesions appeared, and these suggested varicella. Her course was not otherwise remarkable until the end of the third day when she began to vomit and became cyanotic. Vascular collapse developed rapidly and she died en route to the hospital.

Autopsy Report.—Several well-circumscribed ecchymoses were present on the thigh, back, and neck. The lungs were diffusely edematous and firm with decreased crepitation. Small, firm, gray-brown, granular areas were scattered irregularly throughout the lung parenchyma. The splenic and portal veins showed no gross abnormality. The marrow space of a rib was red-brown and moist. Lymph nodes in the retroperitoneal, mesenteric, and mediastinal regions were enlarged to 3.0 cm. Their cut-surface was gray-brown and homogeneous. The liver was enlarged to almost twice the average weight for this age. The surface of the liver contained many small, white, granular areas scattered irregularly at intervals through the parenchyma. These had a maximum dimension of 0.2 cm.

Microscopic examination of the lung showed large, poorly circumscribed areas of edema and necrosis with a striking paucity of inflammatory reaction. Large masses of rod-shaped bacteria were present within the alveoli. Only a few mononuclear cells were found.

Within the liver, isolated foci of complete necrosis without inflammatory reaction were identified. Rod-shaped bacteria, similar to those found in the lung, were also present in these areas of the liver.

The marrow space of the rib was markedly depleted of all marrow elements (Fig. 5). There were clusters of mature lymphocytes with focal aggregation into germinal centers. There were many large cells with multilobed nuclei identified as megakaryocytes, and other large cells identified as young fibroblasts.

DISCUSSION

The diseases in these infants were manifest by two different hematologic responses. They terminated with a common anatomic lesion consisting of decreased cellularity, megakaryocytic hyperplasia, and fibrosis of the bone marrow. The stimulating factor is unknown but is considered a myelo-stimulatory factor which may be activated by a wide variety of agents.

The illness of the first patient resembles most closely that of leukemia, particularly with respect to the presence of circulating immature cells. The second appears to have had a hypersplenic syndrome associated with a congestive splenomegaly of undetermined etiology.

It is thus suggested that myelofibrosis can be the evolutionary end product of a disease state, the nature of which creates a chronic demand on the bone marrow which then becomes functionally incapable of meeting these demands. This results in functional failure of the bone marrow and this is expressed anatomically by myelofibrosis and myeloid metaplasia.

Death due to the underlying disease process may occur in any phase of the syndrome. Therefore, tissue examination, depending upon the stage of the disease, reveals diffuse hyperplasia, hypoplasia, myeloid metaplasia or fibrosis.

Eight cases of myelofibrosis in childhood were discovered in the medical literature. The clinical data of these children have been summarized in Table I. Six of the 8 patients were female, and all were under 3 years of age. Splenomegaly and hepatomegaly were prominent. Anemia was moderate

to severe. The white blood cell count varied from leukopenia to leukocytosis. Immature white cells in the peripheral blood were as frequent as immature red cells. Careful scrutiny of peripheral blood films occasionally revealed a few megakaryocytes. Bone marrow fibrosis was recognized by biopsy in some instances and determined at autopsy in others.

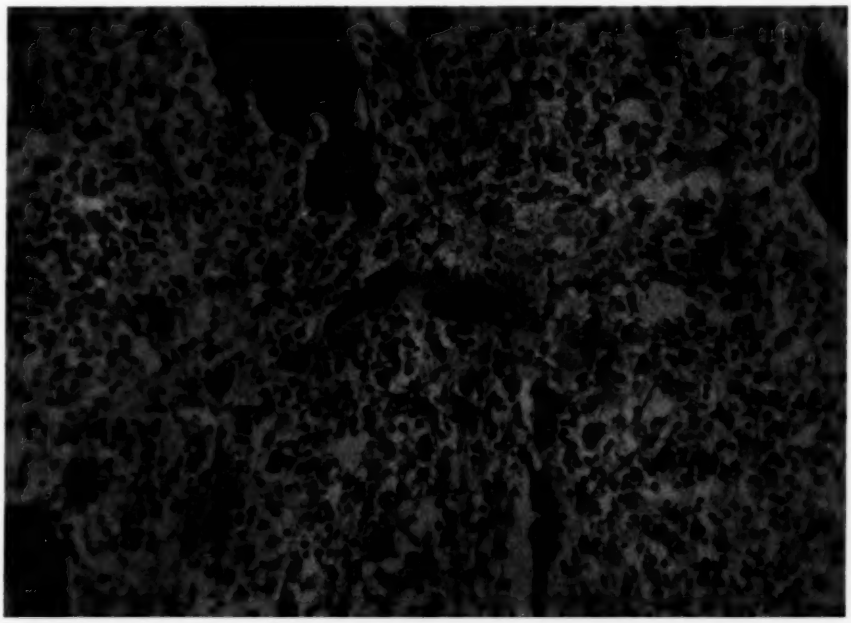

Fig. 5.—On the post-mortem bone marrow of Case 2 there is a striking paucity of cells with retention of the reticulum structure and a prominence of megakaryocytes.

The process of fibrosis of the marrow has been described following x-radiation, tuberculosis infection, Paget's disease, metastatic neoplasm, multiple myeloma, septicemia, and benzene.[3] It has been proposed that focal necrosis of the marrow is initiated which is followed by reactive hyperplasia of the stroma resulting in the sclerosis.[4, 5]

Dameshek[1] made the interesting editorial comment that the bone marrow can proliferate "en masse" as well as along individual cell lines. Thus, fibrosis may be a type of proliferation such as seen in leukemia or polycythemia.

The relationship between myelofibrosis and the myeloid metaplasia may be one of several possibilities: (1) purely fortuitous; (2) myelofibrosis is the result of a primary blood disease, (3) blood diseases are the result of myelofibrosis, (4) the two features are actually similar results of the same noxious agent functioning at two discrete sites,[6] and (5) extramedullary hematopoiesis is a compensatory response.[7, 8] The unusually large number of megakaryocytes has been attributed to an exaggerated physiologic response to a marked decrease in efficiency of platelet formation.[9]

It is only with acceptance of the fourth possibility that this disease can

TABLE I. A SUMMARY OF THE FINDINGS FROM THE

NO.	AUTHOR	AGE (MONTHS)	SEX	SPLEEN	LIVER
1	Rosenthal and Erf[3]	1/12	Female	Enlarged	Enlarged
2	Rosenthal and Erf[3]	1/12	Female		
3	Rosenthal and Erf[3]	10	Female	Enlarged	Enlarged
4	Rosenthal and Erf[3]	1 1/12	Female	Enlarged	Enlarged
5	Erf and Herbut[19]	2	Female	Enlarged	Enlarged
6	Churg and Wachstein[17]	2 8/12	Female		
7	Block and Jacobson[7]	2 9/12	Male	Enlarged	Enlarged
8	Wood and Andrews[2]	2 9/12	Male	Enlarged	Enlarged

be considered a part of the myeloproliferative group.

It has been suggested that splenectomy, while causing no demonstrable hematologic improvement, does not necessarily prove deleterious to the course of the disease.[10] The implication is that metaplasia is not a compensatory mechanism, but a basic feature of the process.

The resemblance of the disease to leukemia may be striking. Suggestions have been made concerning a possible relationship which parallels the "en masse" proliferation of Dameshek. These include the idea that the fibrosis is due to neoplasia of the immature multipotential mesenchymal cell.[11-15]

The histology of the spleen resembles that of granulocytic leukemia although there are differences.[16] The lymphoid follicles in leukemia are obliterated. The lymphoid follicles in myeloid metaplasia are preserved, but occasionally contain a fibrotic process similar to that in the marrow. Many megakaryocytes are present in myeloid metaplasia. There is no invasion by sheets of uniform cells which is unlike leukemia.

Churg and Wachstein described 97 cases of leukemia including 6 in which there was myelosclerosis.[17] In striking contrast to this, a much higher incidence of sclerosis was found in what they described as "non-leukemic myelosis." Furth's[18] definition of leukemia states that "the essential change in leukemia resides in the cell and consists of an acquired inability of immature leukocytes to respond to forces normally regulating their proliferation and maturation."

There is no apparent escape from normal regulation, as defined by Furth, when marrow tissue responds by necrosis to a noxious agent followed by fibrosis. Proliferation of the remaining marrow may or may not be along normal lines of evolution, and this depends upon whether or not the stimulus to necrosis was leukemia. It is suggested that leukemia can terminate with myelofibrosis but so can any disease in which bone marrow failure is a component.

SUMMARY

The clinical history and autopsy findings are presented in 2 children with disease of bone marrow and spleen. In one, there was myelofibrosis of the bone marrow with myeloid

MEDICAL LITERATURE OF EIGHT CHILDREN WITH MYELOFIBROSIS

HEMOGLOBIN	RBC (AS 10^6)	WBC (AS 10^3)	IMMATURE FORMS IN THE PERIPHERAL BLOOD	BONE MARROW	
				BIOPSY	AT AUTOPSY
20%	1.12	10.0	Granulocytic and erythrocytic	Fibrosis	
16%	1.05	7.1	Granulocytic	Fibrosis	
12%	1.09	1.9		Fibrosis	
22%	1.5	1.7	Granulocytic and erythrocytic	Fibrosis	Fibrosis
21%	1.6	6.0 7.2	Erythrocytic	Fibrosis Fibrosis	Fibrosis
9.0 Gm./100 ml.	3.9	17.0	Granulocytic and erythrocytic	Fibrosis	Fibrosis
55%	1.1	15.0	Granulocytic and erythrocytic		Fibrosis

metaplasia of the spleen. The second patient had a change from hyperplasia of the bone marrow to hypoplasia. In each instance there was a prominence of megakaryocytes. Death was associated with disseminated agranulocytic abscesses.

It is proposed that these individuals represent phases in the development of myelofibrosis in which bone marrow progresses from hyperplasia to fibrosis and myeloid metaplasia occurs in the spleen under the influence of unknown forces.

Eight other instances of this syndrome in infants and children are tabulated.

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VARIATION IN THE ROENTGENOGRAPHIC DENSITY OF THE OS CALCIS AND PHALANX WITH SEX AND AGE

HARALD SCHRAER
UNIVERSITY PARK, PA.

INTRODUCTION

ALTHOUGH the marked changes that occur in the size and shape of the skeleton during growth can be observed by the use of roentgenograms,[1] the concomitant changes in the bone mineral concentration, which may also occur during growth, have not been extensively studied due chiefly to the lack of quantitative roentgenographic techniques. With the development of photodensitometric techniques, quantitative measurements of the bone mineral concentration have become possible.[2, 3, 4] The application of this technique for the study of osseous disorders and the normal variation in bone density found in man is relatively unexplored. McFarland[5] published bone density values for the os calcis of 1,200 normal persons of all ages and both sexes. A study with aged subjects (60-98 years) showed that no significant photodensitometric differences occurred in the os calcis and phalanx 5-2.[6] In the latter two studies, the apparatus used was the same as that employed in the present report. Using a different technique and apparatus, Mainland reported that no significant difference in the roentgenographic density occurred in the os calcis,[7] the radius, the lunate, the capitate and the metacarpal bones due to age or sex. Phalanx density, however, showed a decrease with increasing age.[8]

The investigation of photodensitometric bone values in normal subjects according to age and sex would provide a basis for determining the influence of these factors on bone density. As the initial phase in such a study, the results of bone density evaluations made from roentgenograms of the os calcis and phalanx 5-2 in several hundred boys and girls are presented.

METHODS

Roentgenograms of the left os calcis and phalanx 5-2 were taken of subjects in various geographical locations. The number of subjects from each location is shown in Table I.

TABLE I. THE GEOGRAPHIC DISTRIBUTION OF THE SUBJECTS

LOCATION	OS CALCIS FILMS		PHALANX FILMS	
	MALE	FEMALE	MALE	FEMALE
Washington	177	164	173	156
Montana	38	46	41	53
New Mexico	20	26	19	25
Pennsylvania	482	506	304	74
Miscellaneous (U.S.)	21	4	87	87
Totals	738	746	624	395

Biophysics Laboratory, The Pennsylvania State University, College of Chemistry and Physics, University Park, Pa.

This investigation was supported in part by a research grant (A-1292) from the National Institute of Arthritis and Metabolic Diseases, Public Health Service.

Film Exposure Technique.—The bone density computing apparatus, the x-ray technique, and the film developing procedure are standardized and have been described in previous publications.[2, 9] In brief, 8 × 10 no-screen film in cardboard holders are exposed at 55 KVP. The MAS is varied with focal film distance and size of object. The computing machine is used to evaluate the mass of bone in a cross-sectional slice of bone and surrounding flesh from the roentgenographic image. The anatomic section evaluated is referred to as a trace path. The films require that a standardized wedge be exposed on the film adjacent to the anatomic part of interest.

The Standard Wedge.—The standard wedge is precision tooled from an alloy consisting of 92.8 per cent of aluminum and 7.2 per cent of zinc. It is 14 cm. long, and 1.4 cm. wide at the widest part with a slope of 0.1. A frame of the same material holds the wedge. Several of these wedges have been made from a single mass of homogenous material to ensure uniformity between wedges and to permit direct comparison to be made by different investigators who use this technique. The x-ray absorption properties of the wedge material approximates that of bone ash, has good mechanical and chemical stability, and is not difficult to machine.[10]

Bone Sites Evaluated.—The value for the os calcis is obtained from measurements made along a trace path extending from the posterior-superior angle to the anterior-inferior angle of the bone image. Three cross-sectional slices of the phalanx are evaluated, one at the distal and proximal ends and one at the center. The values of the distal and proximal ends are usually averaged and the result is termed the bone density coefficient for the phalanx end trace paths. The values for each end could be presented separately. The center cross-sectional slice is termed the phalanx center trace path.[9]

Soft Tissue Correction.—To evaluate the density coefficient or mass coefficient of bone sections in living subjects, the absorption of x-radiation by under- and overlying soft tissue must be taken into account. The method which has been developed will be explained by reference to Fig. 1. In this case the roentgenogram has been made at right angles to the face of the diagrammatic object. The flesh alone is responsible for the roentgen ray absorption in Areas 1 and 4, whereas bone plus under- and overlying soft tissue are responsible for the absorption in Areas 2, 3, and 5. Therefore, the portions of the trace shown in the lower part of the diagram can be assigned, respectively, to soft tissue and to bone and soft tissue. Then, on the assumption that the soft tissue areas in the regions 2 and 3 underlying and overlying the bone have the same absorbing properties, a soft tissue correction term is subtracted from the area of the central trace, designated as 2, 3, 5, to determine that portion of the trace area which is due to the x-ray absorption by bone alone. The mass coefficient or density coefficient of the bone is then calculated. The term density coefficient is used rather than density, as the value obtained with the machine has to be multiplied by a constant to give the density.

The density coefficient of an object (bone section or soft tissue section) is defined as the number of grams of

the aluminum-zinc alloy, which in a similar geometric shape would absorb the same amount of x-radiation as the object, divided by the volume of the object in cubic centimeters. When the volume of the object is not considered, the mass coefficient is obtained.

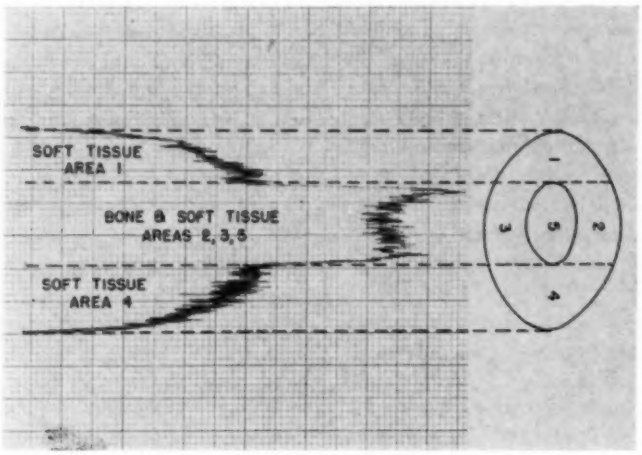

Fig. 1.—Diagrammatic representation of a bone and surrounding flesh with a photodensitometer trace (see text for explanation).

Referring again to Fig. 1, the following gives the computation procedure:

1. The total volume of soft tissue in portions 1 and 4 of the cross-sectional slice is estimated; the shape and dimensions of the soft tissue are estimated from the image on the film.
2. The volume of bone in portion 5 of the cross-sectional slice is estimated also from measurements on the film.
3. The total volume of soft tissue in portions 2 and 3 of the cross-sectional slice is estimated similarly.
4. The average density coefficient of portions 1 and 4 is found by dividing the mass coefficient (determined from the counter reading of the computing machine) of these portions by their volume as estimated in step 1. The result is termed the x-ray density coefficient of soft tissue.
5. The x-ray mass of portion 5 (bone) is found by subtracting from the total mass of portions 2, 3, and 5 (as determined by the computing machine from the central portion of the trace) the x-ray mass of overlying and underlying soft tissue, portions 2 and 3 of the cross-sectional slice. The mass of sections 2 and 3 is determined by multiplying the soft tissue x-ray density from step 4 by the estimated volume of soft tissue in portions 2 and 3 (from step 3).

The foregoing procedure has been in use for several years. Each bone site requires a different calculation for estimating the volume. The methods

presently available for estimating the volumes of the various portions of the cross-sectional slice are more time consuming and considerably less precise than the mass determinations made from the film by the computing machine. Methods of estimating bone and soft tissue volumes, however, are being improved constantly.

The data resulting from the film evaluations were subdivided on the basis of the bone site evaluated, the age and the sex of the subjects. Only films of normal, white subjects which were satisfactory from the standpoint of technique were included. The ages of the subjects used in this study ranged from 7-20 years (Table II).

tabulated as shown in Table II. The interrelationships of the group values are graphically shown in Fig. 2 which presents the mean values and the standard error for each group.

Analysis of the data revealed that (1), with the exceptions noted below, the mean bone density coefficient for each trace path increases significantly with age ($P > .001$). The exceptions were, that there was no significant difference in the phalanx center trace path for males between the 7-9 year group and the 10-12 year group, nor for the os calcis trace path of the females between the 13-15 year group and the 16-20 year groups; (2) the values for the female phalanx are sig-

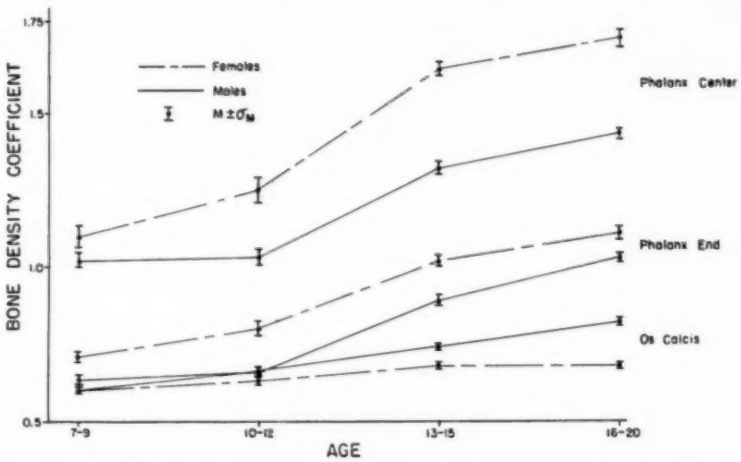

Fig. 2.—The variation in bone density coefficients of the os calcis and phalanx trace paths with sex and age.

RESULTS

The results were grouped by sex and trace path corresponding to the following age ranges of the subjects; 7-9 years, 10-12 years, 13-15 years, and 16-20 years. The mean bone density coefficient and the standard deviation for each group was then calculated and

nificantly greater ($P > .001$) than for the males of the same age; (3) the values for the male os calcis in the 13-15 and 16-20 year groups are significantly greater at the 0.001 level than for the females of the same age, while the male os calcis values are significantly greater at the 0.01 level in

TABLE II. MEAN DENSITY COEFFICIENTS OF THE OS CALCIS AND PHALANX OF SUBJECTS AGED 7 TO 20 YEARS

AGE GROUP	OS CALCIS						PHALANX END						PHALANX CENTER					
	MALES			FEMALES			MALES			FEMALES			MALES			FEMALES		
	MEAN	SD	NO.	MEAN	SD	NO.	MEAN	SD	NO.	MEAN	SD	NO.	MEAN	SD	NO.	MEAN	SD	NO.
7-9	0.60	0.09	138	0.60	0.09	139	0.64	0.11	77	0.71	0.16	97	1.02	0.23	77	1.10	0.21	97
10-12	0.67	0.10	183	0.63	0.08	138	0.66	0.16	101	0.80	0.18	56	1.03	0.28	101	1.25	0.30	56
13-15	0.74	0.10	254	0.68	0.10	296	0.89	0.21	225	1.02	0.18	135	1.32	0.30	225	1.64	0.22	135
16-20	0.82	0.05	163	0.68	0.09	173	1.03	0.19	221	1.11	0.18	107	1.43	0.24	221	1.74	0.31	107

the 10-12 year group. However, there is no noticeable sex difference for this trace path in the 7-9 year groups; (4) the phalanx center trace path, which contains mainly compact bone, shows the highest values with the phalanx end trace paths and os calcis giving lower values, respectively; and (5) the range of values is much greater for each phalanx trace path than for the os calcis trace path.

DISCUSSION

The results of the present study indicate that sexual dimorphism exists in young adults with respect to bone density coefficients obtained from roentgenograms of the os calcis and phalanx 5-2; females have denser phalanges than males in the age groups studied, while males have a denser os calcis. The concept of sex and age differences in bone density has been demonstrated in rats by others using water displacement techniques; females had denser femurs than males and young animals had denser bones than old animals.[11]

Some of these observations may be explained by the earlier maturation of the female skeleton. The earlier closure of the epiphyses in the female and the consequent curtailment of growth appears to accompany an increase in bone mineral concentration as indicated by the higher bone density coefficients observed for the female phalanx. However, this does not account for the higher values found for the male os calcis. It seems unlikely that greater activity on the part of the males could account for this difference. It is conceivable that a different rate of mineral accretion occurs in different bones influenced by hormonal and genetic factors. In mice, for example, it has been shown that estrogen administration induces a hypercalcification of the skeleton in general, while the pubic bones undergo resorption.[12]

The gradual increase in bone density coefficients in both sexes with age appears to reflect classical growth patterns. Prepuberal "density" spurts apparently occur in the phalanx, as can be seen in Fig. 1, between the 10-12 and 13-15 year age groups. An increasing divergence of the mean os calcis values between the males and females is also clearly indicated in the same figure. It should be pointed out that while, in general, the mean bone density coefficients for each trace path increase significantly with age and differ significantly by sex, the magnitude of the standard deviations is such that an individual set of values cannot serve to designate the sex and age of the subject except in extreme cases.

The relationship of the values in the 16-20 year groups, shown in Fig. 2, suggest that the density coefficients of the phalanx center and the os calcis will continue in a like manner for at least part of the third decade. This, of course, can only be shown by further study which is contemplated. It is interesting to note that Mainland[7] found no significant difference in the mean roentgenographic density of the os calcis of 42 men aged 20-54 years and 10 women aged 19-30 years, nor did his data for the men demonstrate a relationship for bone density and age. In a later study, the same author did observe a significant negative correlation with age in phalanx density for 41 men, but did not find a sex difference when compared with 10 women. Other hand bone values (radius, lunate, capitate, and metacarpal) were significantly lower for the women.[8]

Since the age ranges of the subjects, the soft tissue correction, the exposure standard and the densitometric apparatus are different, no direct comparison with Mainland's results can be made.

Williams and associates[13] who used an os calcis technique similar to that developed in this laboratory reported that, although in young normal adults the bone density values reflected the over-all past nutritional history of a subject, marked temporary changes in calcium intake did not alter the bone values.

The apparatus and technique employed in making these measurements are probably an important factor in considering the results. Indicative of the sound chemical and biological basis of the present technique is the correlation coefficient of 0.99 obtained when the mineral content of rat bone samples was compared with the x-ray mass coefficient of the same sample.[14] In addition, when values from x-ray films of intact rat femurs were compared with film values of the same femurs excised, a correlation coefficient of 0.95 was obtained.[15] While no well-controlled studies with human beings have been undertaken to establish the minimal detectable bone density changes which can be observed with this technique, studies with young rats have demonstrated that a severe change in the dietary calcium level can be detected in 7 days or less.[14]

An extension of these studies to cover the span of life is planned. The compilation of adequate bone density coefficient values based on age and sex may serve as standards in studying normal biologic variations. It may also be possible to detect pathologic conditions involving bone, and recovery from osseous disorders which are reflected in the measurable bone sites.

SUMMARY

Using standardized roentgenograms, the x-ray density coefficients of the left os calcis of 738 boys and 746 girls, and the middle and end sections of the second phalanx of the left fifth finger in 395 girls and 624 boys, all between the ages of 7 and 20 years, were measured. Significant differences in the mean values were noted which were associated with the age and sex of the subjects.

Analysis of the data revealed that:

1. The mean density coefficient of both bones increases significantly with age in both sexes except for the os calcis trace path of the females between age groups 13-15 and 16-20 and the phalanx center trace path of the males between age groups 7-9 and 10-12.

2. The phalanx shows higher density coefficients than the os calcis in both sexes.

3. The phalanx density coefficients of the females are significantly greater than those of the males of the same age and, except for the 7-9 year age group, the os calcis values of the males are significantly greater than those of the females.

The author wishes to acknowledge the labors of the late Dr. Walter N. Brown, Jr., formerly of this laboratory, who collected much of the present material.

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MUMPS MENINGOENCEPHALITIS IN CHILDREN

BAIRD S. RITTER, M.D.
SOUTHBURY, CONN.

MENINGOENCEPHALITIS, occurring in association with infection by the mumps virus, is an acute inflammatory disease of the central nervous system due in most instances to direct invasion of the brain and meninges by the specific virus.[1, 2] In some cases, however, the demyelinating or leukoclastic encephalitis found with mumps infection can be due to an allergic reaction by the brain occurring in the course of the disease.[2, 4-7] The central nervous system manifestations of mumps may precede, occur simultaneously with, or follow salivary gland involvement, or the central nervous system manifestations may occur without any other clinical evidence of mumps infection.[3, 8-16] This intriguing variability in the relationship between meningoencephalitis and other clinical forms of mumps led us to review our cases of mumps meningoencephalitis.

The purpose of this paper is to summarize our experience with 30 cases of mumps meningoencephalitis occurring in children under 14 years of age. Special emphasis will be placed upon the epidemiological, clinical, and serologic features of the disease.

METHODS AND MATERIALS

The records of all cases of mumps meningoencephalitis admitted to the Pediatric Service of the George F. Geisinger Memorial Hospital and Foss Clinic from January, 1951, to January, 1956, were reviewed. The Pediatric Service at this institution cares for children from birth to 14 years of age.

Lumbar punctures were done on admission on all of the patients. The cerebrospinal fluids were examined for cell, protein, and sugar content. Routine cultures for bacteria were done on all spinal fluids within 30 minutes of obtaining the specimens by inoculating the centrifuged sediment into brain-heart infusion broth with 2 per cent rabbit's blood and by streaking the sediment on blood agar plates made from blood agar base plus 5 per cent rabbit's blood. These cultures were all negative for bacterial growth after 48 hours' incubation at 37° C. under reduced oxygen tension. Ten of the 30 cases had acid-fast cultures made by streaking Petragnani medium with sediment of the cerebrospinal fluids. All of these cultures were negative for growth of acid-fast bacilli after 6 weeks' incubation at 37° C.

Intracutaneous tuberculin tests in concentrations of 0.0002 mg. and 0.005 mg. of purified protein derivative were done on all patients. The tuberculin tests were negative in every case except for one child who had a reaction at 48 hours greater than 6 mm. of edema to 0.005 mg. of PPD. This

From the Department of Pediatrics, the George F. Geisinger Memorial Hospital and the Foss Clinic, Danville, Pa.

child was considered to be a positive tuberculin reactor. The patient's chest x-ray showed a pulmonary calcific density thought to represent a healed primary tuberculous complex. Cultures of the cerebrospinal fluid and gastric washings of this patient were negative for the tubercle bacillus and the clinical course of the illness was characteristic of mumps meningoencephalitis.

Paired sera were obtained from 24 patients for complement fixation tests against mumps antigens. All mumps serologic tests were performed by the Virus Diagnostic Laboratory of the Children's Hospital of Philadelphia.* The methods of preparing the mumps antigens and of performing the complement fixation tests which were used by this laboratory have been described.[13, 17]

A meningoencephalitis was considered to be present if the cerebrospinal fluid showed a pleocytosis of 10 or more leukocytes per cubic millimeter. The cases were diagnosed as mumps meningoencephalitis by the occurrence of clinical parotitis prior to, concomitant with, or shortly following the onset of the central nervous system manifestations or, in the absence of parotitis, by the presence of significantly rising complement fixing antibodies against the mumps virus in paired sera. Patients suspected clinically of having mumps meningoencephalitis but in whom pleocytosis of the cerebrospinal fluid did not occur were not included in this study.

The severity of illness was judged by the clinical findings on initial admission examination and by the subsequent hospital course. The children were described as not sick at all when they had no temperature elevations, were alert, and well oriented; as mildly ill when they had moderate temperature elevations, were only mildly lethargic, and well oriented; as moderately ill when they had higher fevers, were moderately lethargic and well oriented; as severely ill when they had high temperatures, marked lethargy or stupor, and disorientation or convulsions.

*The performance of these tests is a public service available to all hospitals in Pennsylvania. During the period of this study, the laboratory was supervised by Dr. Werner Henle.

RESULTS

During this study, 30 cases of mumps meningoencephalitis were diagnosed. The age range of the children was from 2 to 14 years. The average age of the sick children was 7.4 years which approximates the reported age peak of 6 years for mumps parotitis.[11, 18] There was no difference in the average age of the patients with meningoencephalitis with parotitis (7.7 years) and of the patients without parotitis (7.0 years). Males constituted 19 (63 per cent) of the total number of cases.

The seasonal incidence of the cases in this series is presented in Fig 1. Cases were diagnosed in every season of the year, but the disease had its highest incidence in the spring and summer. Of interest is the fact that meningoencephalitis with parotitis was most frequent in the spring and meningoencephalitis without parotitis was most frequent in the summer.

The clinical manifestations of mumps meningoencephalitis are those characteristic of a widespread acute inflammation of the brain and of the meninges. These manifestations include symptoms and signs of encephalitis, i.e., headache, vomiting, lethargy,

and convulsions, plus symptoms and signs of meningitis, i.e., stiff neck and spinal fluid pleocytosis. Table I indicates the most frequent symptoms and signs which occurred in these 30 cases of mumps meningoencephalitis together with the incidence of similar manifestations reported by Henle[13] and by Enders.[19]

Of the 30 cases of mumps meningoencephalitis, in 13 (43 per cent) there was no parotid, submaxillary, or sublingual swelling. The proof of infection by the mumps virus was made in these 13 cases by rising serologic titers against the mumps virus in paired sera from each patient. The other 17 patients (57 per cent) had parotitis at intervals ranging from 9 days before to 5 days following the appearance of the central nervous system manifestations. Three children were admitted with symptoms and signs of meningoencephalitis and their parotid swelling developed later in the course of the illness. These 3 cases plus the 13

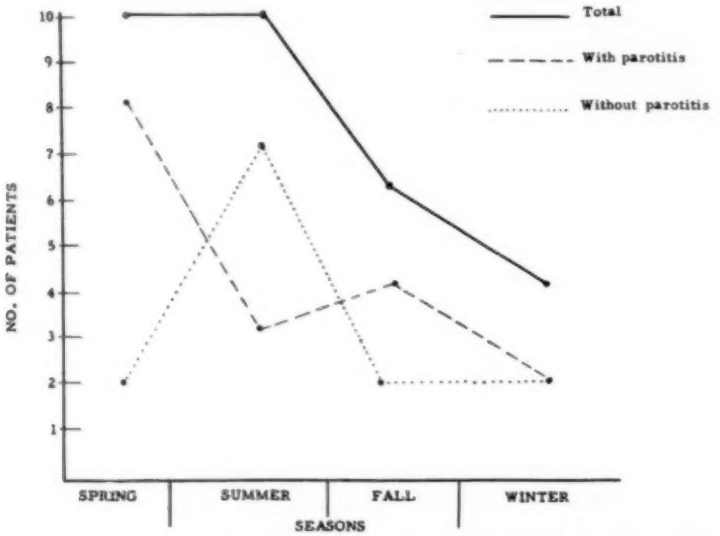

Fig. 1.—Seasonal incidence of mumps meningoencephalitis with and without parotitis.

TABLE I. SYMPTOMS AND SIGNS OF MUMPS MENINGOENCEPHALITIS
(FIGURES STATED AS PERCENTAGE OF TOTAL GROUP)

SYMPTOMS AND SIGNS	PRESENT STUDY (30 CASES)	KANE AND ENDERS[19] AND HENLE ET AL.[13] (COMBINED TOTAL, 107 CASES)
Headache	66.6	59.9
Vomiting	73.3	65.8
Lethargy	50.0	26.7
Convulsions	10.0	13.0
Abdominal pain	13.8	20.7
Nuchal rigidity	63.6	62.4
Positive Kernig and/or Brudzinski	30.0	26.7

cases in which parotitis never occurred produced 16 cases (53 per cent) in which the etiologic diagnosis was not ascertainable at the time of hospital admission.

There were no cases of sublingual or submaxillary adenitis and no instances of orchitis in the 30 cases.

Abdominal pain was a persistent and severe complaint in 4 children. Serum amylase determinations were performed on sera from these 4 patients and 3 of them had elevated titers, i.e., 227, 326, and 560 units per 100 ml. of serum, respectively. (Normal value—50 to 150 units per 100 ml. of serum.) Since elevated serum amylase titers can occur with parotitis in the absence of pancreatitis, these 3 patients were considered on clinical grounds to have mumps pancreatitis. Each of these patients also had parotitis.

The severity of the illness varied. On admission, 2 of the children did not appear ill. One of these was admitted for investigation of falling spells, the other because of a questionably stiff neck in an afebrile child. The remaining children were categorized as follows: 7 were mildly ill, 17 were moderately ill, and 4 were severely ill. Two of the severely ill children had generalized convulsions.

Fever of 101° F. or higher rectally was present on admission in 26 of the 30 patients. Two of the remaining 4 patients gave a history of having had significant temperature elevations prior to admission but did not have fever on admission or subsequently during the hospital course. The total duration of fever above 101° F. rectally was from zero to 9 days, with an average of 5.3 days. By the time temperatures were below 100° F. rectally, the children appeared clinically well. No complications were observed during the course of illness in any of the cases.

A summary of the cerebrospinal fluid findings and peripheral blood cell counts will be found in Table II. There was no correlation between the height of the cerebrospinal fluid cell count and the severity of the illness. Repeat lumbar punctures were done if the clinical course was prolonged or seemed unusual. Pleocytosis in the spinal fluid persisted as long as 30 days after the onset of the meningoencephalitis.

The treatment was principally symptomatic and supportive. Rest, hydration, measures to control high fever and convulsions, and treatment of concurrent infections were used. Intravenous fluids were necessary for periods of 24 to 48 hours because of vomiting or dehydration in 19 of the children. Antibiotics were administered to 24 of the 30 patients until the

TABLE II. DATA ON CEREBROSPINAL FLUID AND BLOOD STUDIES IN 30 CASES OF MUMPS MENINGOENCEPHALITIS

COMPONENT	AVERAGE	RANGE	PER CENT OF CASES ABNORMAL	NORMAL VALUES
WBC in CSF (Cells/c.mm.)	357	15-1212	100	<10
Per cent lymphocytes in CSF	89	30-100*	—	—
Total protein in CSF (Mg./100 ml.)	48.5	17-140	50	<40
WBC in blood (1,000/c.mm.)	9.5	5.4-17	30	5-10
Per cent lymphocytes in blood	34	10-55	—	—

*Only one patient had less than 50 per cent lymphocytes in the CSF.

illness was established as being definitely nonbacterial in etiology. Coincidental bacterial infections were also treated with antibiotics as indicated. Complete bed rest was maintained during the hospitalization period in all cases and gradually increasing activity was permitted during convalescence at home. The average time of hospitalization for all cases was 9.1 days with a range of 5 to 19 days.

Demyelinating or leukoclastic encephalitides are produced as an expression of an allergic reaction by the nervous system during the course of some diseases in experimental animals and ACTH or corticosteroids have been used in preventing the development of some demyelinating encephalopathies under precise experimental conditions.[20, 21] Since it is possible that some cases of mumps meningoencephalitis in human beings are due to an allergic mechanism, adrenocorticotrophic hormone was given to 2 children in this study group. The therapy produced no measurable effect upon the clinical course of the disease.

Follow-up examinations were obtained on all children except one child who was killed in an accident prior to her return visit.

Sequellae appeared in one 6-year-old boy who developed staring spells 2 years after convalescence from mumps meningoencephalitis. The child had an abnormal electroencephalogram evidenced by biparietal and bifrontal spikes occurring in sleep. At the present time his symptoms are partially controlled with diphenylhydration and phenobarbital therapy.

SEROLOGIC STUDIES

Paired blood samples were drawn for serologic studies on 11 of the 17 cases of meningoencephalitis with parotitis and on all of the 13 cases of meningoencephalitis without parotitis. The data on the results of these titer studies are summarized in Tables III and IV.

The sera were tested in each case for complement fixing antibodies against mumps soluble antigen (S antigen), a small molecule attached to the membrane of the chick embryo on which the mumps virus is grown, and against mumps virus antigen (V antigen), a larger molecule attached to the virus particle itself.[13] The antibody titers are expressed as the highest initial dilution of serum which completely fixed complement in the presence of the mumps antigen. The first sera were obtained on an average of 3.5 days after the onset of the meningoencephalitis with a range of 2 to 5 days. The second sera were obtained on an average of 13.3 days after the first specimen was drawn with a range of 5 to 54 days.

It has been stated that a presumptive diagnosis of mumps infection can be made from one serum specimen provided that the mumps anti-S antibody titer is significantly greater than the mumps anti-V antibody titer.[13] Of the 13 meningoencephalitis patients without parotitis, 4 patients (Cases 20, 21, 22, 30) demonstrated a significantly higher* mumps anti-S antibody titer than the mumps anti-V antibody titer in the initial serum. Among the 3 cases in whom parotitis developed following the onset of the meningoencephalitis, one patient (Case 5) had a higher anti-S than anti-V titer in the initial sera. Thus, a total of $\frac{5}{16}$ patients (31.2 per cent) with meningoencephalitis without initial parotitis had

*Defined as a fourfold difference in titer between the two antibodies.

TABLE III. COMPLEMENT FIXATION ANTIBODY TITERS IN 17 CASES OF MUMPS MENINGOENCEPHALITIS WITH PAROTITIS

CASE NO.	AGE (YEARS)	SEX	INITIAL SERUM			SECOND SERUM			TIME RELATIONSHIP OF PAROTITIS TO MENINGOENCEPHALITIS		
			ANTI-S* TITER	ANTI-V† TITER	DAY OF DISEASE DRAWN	ANTI-S* TITER	ANTI-V† TITER	DAY OF DISEASE DRAWN	DAYS BEFORE DISEASE	ONSET WITH DISEASE	DAYS AFTER DISEASE
1	7	M	1:8	1:8	4	1:16	1:32	60		X	
2	6	M	1:8	1:2	2	1:16	1:32	15	4		
3	6	M	—	—	—	—	—	—	7		
4	11	F	—	—	—	—	—	—	1		
5	3	F	1:8	<1:2	3	1:32	1:64	13			4
6	7	M	—	—	—	—	—	—	1		
7	7	F	1:8	1:32	2	1:32	1:64	8	9		
8	11	F	1:64	1:128	5	1:64	1:512	15	3		
9	8	F	1:64	1:16	5	1:64	1:64	13		X	
10	6	M	—	—	—	—	—	—	3		
11	6	M	1:2	<1:2	2	1:16	<1:2	10			5
12	7	M	1:32	1:8	3	1:32	1:64	18	6		
13	11	F	—	—	—	—	—	—	7		
14	7	F	—	—	—	—	—	—	3		
15	9	M	1:64	1:256	4	1:64	1:256	22	9		
16	10	M	1:32	1:32	5	1:128	1:128	13	3		
17	9	M	1:16	1:16	5	>1:64	>1:64	35			4

*Anti-S titer means complement fixation antibody titer against mumps soluble antigen.
†Anti-V titer means complement fixation antibody titer against mumps virus antigen.

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TABLE IV. COMPLEMENT FIXATION ANTIBODY TITERS IN 13 CASES OF MUMPS MENINGOENCEPHALITIS WITHOUT PAROTITIS

CASE NO.	AGE (YEARS)	SEX	INITIAL SERUM			SECOND SERUM		
			ANTI-S* TITER	ANTI-V† TITER	DAY OF DISEASE DRAWN	ANTI-S* TITER	ANTI-V† TITER	DAY OF DISEASE DRAWN
18	9	M	1:4	1:4	3	>1:64	1:64	20
19	11	M	1:8	1:4	2	1:32	1:32	20
20	3	M	1:32	1:4	5	1:32	1:64	13
21	6	F	1:4	<1:2	4	1:16	1:8	11
22	9	M	1:32	<1:2	3	1:32	1:4	10
23	3	M	1:8	1:8	3	1:32	1:128	8
24	6	M	1:8	1:32	2	1:32	>1:128	13
25	2	M	<1:2	<1:2	5	1:128	1:128	13
26	13	F	1:2	1:2	2	1:16	1:128	15
27	2	M	<1:2	1:2	3	1:32	1:32	18
28	7	M	1:64	1:32	4	>1:128	1:128	12
29	9	F	1:64	1:128	5	1:64	1:512	12
30	13	F	1:32	<1:8	2	1:64	1:32	17

*Anti-S titer means complement fixation antibody titer against mumps soluble antigen.
†Anti-V titer means complement fixation antibody titer against mumps virus antigen.

an antibody pattern in the first serum in which the anti-S antibody titer exceeded the anti-V antibody titer.

In the 8 cases in whom parotitis was present before the onset of, or occurred simultaneously with, meningoencephalitis 3 patients (38 per cent) demonstrated this presumptively diagnostic antibody pattern (anti-S greater than anti-V) in the initial serum. Thus, of the 24 children in whom serologic studies were done 8/24 (33.3 per cent) had a higher mumps antisoluble antibody titer than the mumps antivirus antibody titer in the first serum specimen.

All of the 24 patients except one (Case 15), who had parotitis, showed a fourfold or greater rise in the antibody titers against mumps soluble, mumps virus, or both mumps antigens when the second serum titer was compared with the first serum titer. Such an increment in serum titers is considered to be diagnostic of mumps infection.[13, 19]

During the same time interval which this study encompasses, 54 patients with nonbacterial meningoencephalitis in whom the etiological diagnosis was never established were admitted to the Pediatric Service and were studied. Paired serum specimens from 48 of these 54 patients were sent to the Virus Diagnostic Laboratory for analysis and all were reported negative for evidence of current or recent mumps infection. Since almost all patients infected with the mumps virus develop complement fixing antibodies against mumps antigens,[22] it seems reasonable to assume that few, if any, cases of mumps meningoencephalitis without parotitis were not diagnosed during the period of this study.

DISCUSSION

The exact incidence of meningoencephalitis as a complication of mumps infection is unknown. It has been estimated that in 40 per cent of all cases of mumps infection there is no clinical evidence of disease.[22, 23] The reported incidence of meningoencephalitis occurring in epidemics of mumps infection has varied from one to 65 per cent.[24] It is possible that any reported incidence of central nervous system involvement in mumps is misleading since mumps is principally a

benign disease of childhood and only those cases with unusually severe symptoms or with complications are hospitalized and studied.

The predominance of meningoencephalitis with parotitis in the spring and the predominance of meningoencephalitis without parotitis in the summer was observed in this series and in series reported by Henle, Kilham, and Enders.[3, 13, 14, 19] The reason for this seasonal variation is uncertain but some facts are known which bear upon the problem. March and April are the months of highest incidence of clinical parotitis due to mumps[18] and of meningoencephalitis with parotitis. The experimental observations of Johnson and Goodpasture[25] and of Kilham[3] suggest that, in the summer, inapparent parotid infections with mumps virus may serve as the nidus for meningoencephalitis due to the same agent, but why mumps parotitis is frequently a subclinical infection in the summer and a clinical entity during other seasons of the year is still a mystery.

That mumps meningoencephalitis without parotitis is predominantly a disease of summer is of practical importance for it is during this same season that poliomyelitis in both the paralytic and nonparalytic forms occurs with greatest incidence.[14] This seasonal coincidence of nonparalytic poliomyelitis and mumps meningoencephalitis without parotitis makes the differential diagnosis of these similar clinical entities difficult without the use of ancillary diagnostic methods such as the mumps complement fixation test.

The clinical picture and course of our patients did not differ significantly from other reported series of mumps meningoencephalitis with the exception that no neurological complications were observed during the course of illness and sequellae developed in only one patient. There are reports in the literature of complications and sequellae occurring with mumps meningoencephalitis. These include death, optic neuritis, deafness, ocular palsy, hemiparesis, spasticity, isolated muscle weaknesses, quadriplegia, and personality changes.[1, 12, 14, 26] However, the incidence of such complications is low. Ford[27] states that the prognosis for complete recovery is excellent.

Serologic evidence of mumps infection is necessary to determine the etiology of mumps meningoencephalitis without parotitis in lieu of culturing the virus from the patient. Substantiating the etiology of a disease by serologic methods requires the demonstration of significant differences in antibody titers between two sera drawn from the patient, one early and one later in the disease. However, it has been shown that in 60 per cent of cases of subsequently proved mumps meningoencephalitis a presumptive diagnosis of mumps infection can be made from the antibody titers of the first serum sample, provided the anti-S antibody titer is significantly higher than the anti-V antibody titer.[13] This incidence of presumptive diagnosis from a single serum occurs only if the initial serum is drawn within the first week of clinical illness, for the incidence of a presumptively diagnostic serum pattern falls to 40 per cent if the initial serum is obtained after the first week of illness. If there is no significant difference between the antibody titers in paired sera, or if only one serum is obtained, an antibody titer of 1:32 or greater against either or both mumps

antigens enables a diagnosis of recent mumps infection to be made.[13] However, on this basis alone there can be no certainty that the illness under investigation is due to mumps. Confirmation of the presumptive diagnosis requires a second serum showing a fourfold or greater rise in antibody titer against one or more antigens.[13, 19]

The data presented from our cases demonstrate the value of the presumptive single serum, double antigen, complement fixation test for diagnosing mumps meningoencephalitis. A diagnosis of mumps meningoencephalitis from the antibody pattern in a single serum was possible in 32 per cent (5/16) of patients with meningoencephalitis without initial parotitis, and subsequent serologic studies of paired sera proved the correctness of the original etiological diagnosis in all of the patients in whom the diagnosis was made. Thus, the presumptive diagnostic antibody titer pattern, when present, is valid evidence of the presence of mumps infection and is most useful for making a rapid etiological diagnosis in cases of mumps meningoencephalitis without parotitis.

SUMMARY

1. The epidemiology, clinical course, and serologic findings in 30 cases of mumps meningoencephalitis occurring in children under 14 years of age are presented.

2. Thirteen patients did not have parotitis at any time during the course of their meningoencephalitis. Of the remaining patients, 12 had parotitis prior to, 2 had parotitis concomitant with, and 3 had parotitis following the onset of symptoms of central nervous system involvement.

3. Fifty-five per cent of the cases of meningoencephalitis without parotitis occurred in the summer season. Forty-seven per cent of the cases of meningoencephalitis with parotitis occurred in the spring season.

4. A presumptive diagnosis of mumps infection was made in 32 per cent of the cases of mumps meningoencephalitis without parotitis on the basis of the presence of a higher mumps antisoluble antibody titer than the mumps antivirus antibody titer in the initial serum drawn within the first 5 days of illness.

5. Confirmation of the etiological diagnosis was possible in all of the 13 cases of mumps meningoencephalitis without parotitis and in 10 of the 11 serologically studied cases with parotitis by demonstrating a significant rise in the complement fixation antibody titer against mumps soluble or mumps virus antigen in a second serum drawn at least 5 days days after the first serum was obtained.

6. No complications were observed during the course of illness in any of the 30 cases. A convulsive disorder occurred in one patient 2 years after recovery from meningoencephalitis.

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IDIOPATHIC HYPERCHLOREMIC RENAL ACIDOSIS

HANS W. KUNZ, M.D., M. W. CHEUNG, M.D., AND EDWARD L. PRATT, M.D.
NEW YORK, N. Y.

TWO cases of idiopathic hyperchloremic acidosis are presented, one illustrating recovery following prompt recognition and treatment of the disease, and the other demonstrating irreparable renal damage when the nature of the illness was not recognized until the patient was 5½ years old. The salient biochemical abnormalities are shown, and the importance of early diagnosis and appropriate treatment is emphasized.

CASE 1.—J. C. was first seen at the age of 5½ years. The parents and two siblings were living and well. The patient was thriving until she was 2 years of age when she experienced frequent episodes of pyuria. At the age of 4 years polydipsia and polyuria were noted. An intravenous pyelogram one year later demonstrated medullary renal calcifications and an otherwise normal urinary tract. Radiography of the bones was normal.

The available records show that at the age of 9 months the patient was well above the 50 percentile position for weight (9 kilograms) and length (71 cm.). Her physical development then began to fail. At 18 months she was at the 40 percentile (10.7 kilograms, 80 cm.), at 2½ years at the 25 percentile for weight (12.8 kilograms) and 15 percentile position for height (88 cm.), and at 5½ years of age below the 10 percentile position for weight (16 kilograms) and height (106) cm.).

At 5½ years she was physically well, of short and thin body build; the weight was 16 kilograms, the height 106 cm. The physical examination was normal. Laboratory data were: hemogram normal; Mantoux test negative; serum: carbon dioxide content 16.2 mEq. per liter, chloride 115 mEq. per liter, calcium 10.9 mg. per cent, phosphorus 3.94 mg. per cent, and alkaline phosphatase 18.7 Bodansky units. Urinalysis showed: pH (pHydrion paper method) on 4 fresh specimens, 6,7,7,7; albumin negative; sediment normal; maximal specific gravity on urinary concentration test 1.010. She voided 1,300 ml. in 24 hours; the pH of this specimen was 7.08 by electrometric measurement; the titratable acidity was 0.5 mEq., and the ammonia content 49.1 mEq. per 1.73 square meter per day.

The diagnosis of hyperchloremic renal acidosis with secondary renal calcifications was made and the patient was placed on a solution consisting of 200 Gm. sodium citrate, 100 Gm. citric acid, water to 1,000 ml., of which she received 40 ml. per day, providing 5 mEq. of sodium per kilogram per day. She was treated for three months during which time she was well and gained 1.8 kilograms. The serum carbon dioxide reached 18 mEq. per liter and the serum chloride was 108 mEq. per liter. Therapy then was discontinued for one month. During this time she lost 0.2 kilogram of weight, the serum carbon dioxide fell to 14.5 mEq. per liter, and the serum chloride rose to 118 mEq. per liter. In 24 hours

From the Children's Medical Service, Bellevue Hospital, and the Department of Pediatrics, New York University, College of Medicine.

she voided 950 ml., the urinary pH was 7.29 titratable acidity 1.2 mEq., and the ammonia content 21.2 mEq. per 1.73 square meters per day.

During the subsequent 10 months of therapy the serum carbon dioxide varied between 19 and 21 mEq. per liter, the serum chloride dropped to 105 mEq. per liter, the phosphorus was 4.5 mg. per cent, the nonprotein nitrogen was 28.2 mg. per cent, and the alkaline phosphatase dropped to 14.2 and later to 8.8 Bodansky units. There was a weight gain of 5 kilograms. The patient attained the 60 percentile position for weight (22.6 kilograms), and the 35 percentile position for height (117 cm.). She was feeling well.

CASE 2.—T. A. was admitted to Bellevue Hospital at the age of 8 weeks. Father, mother, and a 15-month-old sister were in good health. The patient was born after a normal pregnancy, the birth weight was 3.6 kilograms. He was fed a conventional milk, water, and carbohydrate mixture. Twenty drops of Vi-Penta had been added daily. Projectile vomiting shortly after the feeding had been present almost since birth. Two weeks prior to admission he also developed diarrhea. No medication was given.

On admission the patient weighed 2.4 kilograms, was severely dehydrated, showed muscular hypotonia, and was critically ill. The remainder of the physical examination was within normal limits.

Laboratory data were: hemoglobin 11.5 Gm. per cent, erythrocyte count 4.4 million, leukocyte count 19,000. Urinalysis showed: pH 6.0, albumin 1 plus, Sulkowitch test 1 to 2 plus, and a few white blood cells and hyaline casts in the sediment. The serum carbon dioxide content was 9 mEq. per liter, the chloride 121 mEq. per liter, the sodium 147.5 mEq. per liter, the potassium 4.45 mEq. per liter the nonprotein nitrogen 29.1 mg. per cent, the calcium 11.6 mg. per cent, the phosphorus 4.31 mg. per cent, and the total protein 8.15 Gm. per cent. A gastrointestinal series was normal; radiograms showed some osteoporosis and no evidence of nephrocalcinosis. A glucose tolerance test, a serum electrophoretic pattern, and the formaldehydogenic hormone excretion were normal. A two-dimensional paper chromatogram of a urine specimen showed a normal pattern of amino acids.

Hospital Course.—After correction of the dehydration with parenteral fluids, the patient was placed on an oral solution consisting of 100 Gm. of sodium citrate and 60 Gm. of citric acid in 1000 ml. This mixture was administered in a dose of 12 to 60 ml. per day, providing an average of 5 mEq. of sodium per kilogram per day until the patient reached 21 months of age. Alkali therapy was then discontinued. After a short period of acidosis and arrest of weight gain but no other clinical manifestations, the weight gain was resumed and the values for serum bicarbonate and serum chloride remained fairly stationary at normal levels. The weight at the age of 2 years was 11 kilograms.

During the first few weeks of hospitalization the following observations were made: (1) Discontinuance of citrate therapy resulted in arrest of weight gain, and reappearance of vomiting and acidosis. (2) Replacement of part of the sodium by potassium citrate did not change the muscular hypotonia, the serum potassium level, or the electrocardiogram. The patient became more acidotic. Potassium was therefore discontinued. (3) Treatment with monosodium-dihydrogen phosphate (400 mg. phosphorus daily) produced arrest of weight gain, humoral acidosis, a large increase in urinary phosphorus excretion, but no change in urine pH.

Throughout the observation of the patient it was noted that he was extremely susceptible to infections which were accompanied by extensive shifts in the water and electrolyte metabolism. The weight dropped immediately from minor infections, and parenteral fluids had to be used liberally to prevent or correct acidosis.

TABLE I

DATE	SERUM (mEq./L.) CO_2	SERUM (mEq./L.) CL	THERAPY	URINE pH	URINE AMMONIA (mEq./1.73 M²/DAY)	URINE TITRATABLE ACIDITY (mEq./1.73 M²/DAY)
2-15-51	9	121	Na citrate			
3- 5-51	21.6	110	Na Citrate			
3-16-51	16	114	None	6.2	78	16
3-19-51	18.4	110	None	6.2	45	13
3-21-51	22	110	None	6.2	63	15
3-28-51		118	None	6.7	19	7
4-13-51	18	109	None	6.1	45	19
4-19-51	19.8	107	None	7.1	32	7
4-25-51	21.8	102	NaH_2PO_4	6.3	35	40
5- 1-51	21.6	102	NaH_2PO_4	6.1	32	31
5- 7-51	20.7	108	NaH_2PO_4			
5-14-51	14.5	118	NaH_2PO_4	6.2	50	29
5-21-51	18.9	105	Na Citrate			
6-11-51	18	108	Na Citrate			
6-18-51	18	108	Na and K	7.2	8	24
6-25-51	15.3	118	Citrate			
7- 6-51	13.5	113	Citrate			
7-12-51	17.1	111	Na Citrate			
8-13-51	17	97	Na Citrate			
9- 4-51	20.4	104	Na Citrate	7.8	13	0
11-13-51	23.4	109	Na Citrate			
12- 9-51	20.3	100	Na Citrate			
2-18-52	20.7	107	Na Citrate	8.2	0	0
2-21-52	17.1	111	None			
2-25-52	15.7	130	None	5.8	45	47
2-29-52	17.5	108	Na Citrate			
3-27-52	18.9	118	Na Citrate			
5-27-52	19.8	109	Na Citrate			
7-24-52	22.5	104	Na Citrate			
9- 4-52	20.7	112	Na Citrate			
10- 6-52	17.1	110	None			
10-11-52	16.2	113	None			
10-17-52	15.3	115	None			
10-24-52	20.7	112	None			
10-31-52	20.7	112	None			
12-10-52	18.9	114	None	6.7	37	11
1- 7-53	19.3	109	None	6.2	54	26

The most consistently abnormal laboratory finding was a low titratable acidity and ammonia exeretion in the urine, accompanied by a relatively high urinary pH (Table I, Fig. 1).

DISCUSSION

Clinical Aspects.—

Natural course: Idiopathic hyperchloremic renal acidosis is caused by a renal tubular defect of conservation of fixed base, resulting in a metabolic acidosis and exeretion of urine of a higher pH than expected in the presence of metabolic acidosis. It begins at or shortly after birth. The severity of symptoms depends on the degree of the defect. In severe cases the diagnosis is established in infancy after chemical investigation of failure to thrive, muscular hypotonia, constipation, anorexia or vomiting.[1-19] Without proper therapy, the disease results in

death from dehydration and acidosis or intercurrent infection. If it is treated properly for weeks or months, spontaneous recovery seems to ensue. Patients with a mild form of this disease are apt to be overlooked in infancy and the diagnosis is made only in later childhood or adult life,[20-31] after renal deposition of calcium has caused secondary damage to the distal tubules and demineralization of the skeleton. Polydipsia and polyuria or a renal stone may be the first symptoms; or an intravenous pyelogram, because of repeated urinary infections, may show nephrocalcinosis; or radiography of the bones may demonstrate changes secondary to chronic acidosis (osteoporosis, osteomalacia, late rickets).

Diagnosis: The diagnosis of hyperchloremic renal acidosis may be suspected when the kidneys fail to produce a urine as acid as that observed in comparable "normal" infants when they are placed under the stress of a comparable degree of metabolic acidosis, and when other renal disorders have been eliminated by urine culture, intravenous pyelography, etc.

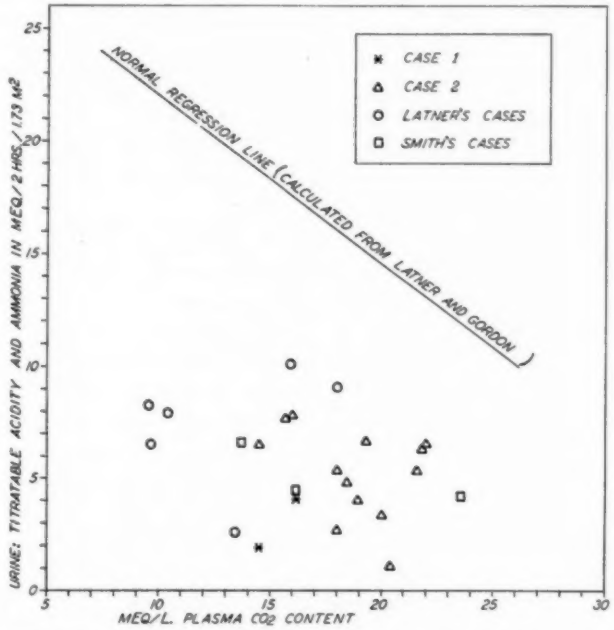

Fig. 1.—Deficiency of renal base economy. Values fall below normal regression line.

Differential diagnosis: Table II lists the clinical differential diagnostic considerations and the principal feature in their distinction from idiopathic hyperchloremic renal acidosis.

In the differential diagnosis of the biochemical abnormality of hyperchloremia, lowered plasma carbon dioxide, and relatively high urinary pH, consideration must be given to abnormal

TABLE II. DIFFERENTIAL DIAGNOSIS OF IDIOPATHIC HYPERCHLOREMIC RENAL ACIDOSIS

DISEASES	DIFFERENTIATING CRITERIA
Improper feeding technique:	
Vitamin D intoxication	History, chemical investigation
Underfeeding:	
Deficiency in calories, protein, or vitamins	History
Anomalies of gastrointestinal tract:	
Esophageal or pyloric anomalies	Radiography
Congenital megacolon	Radiography
Intermittent volvulus	Radiography
Malrotation of intestine	Radiography
Renal diseases:	
Congenital anomalies	Radiography
Infections	Urinalysis
Renal diabetes insipidus	Chemical and hormone investigation
Central nervous system disturbances:	
Brain injury	History
Subdural effusion	Subdural taps
Endocrine disturbances:	
Hypothyroidism	Chemical and hormone investigation
Hypoadrenalism	Chemical and hormone investigation
Hyperparathyroidism	Chemical and hormone investigation
Metabolic diseases:	
Fanconi syndrome	Chemical investigation
Idiopathic hypercalcemia	Chemical investigation
Hypophosphatasia	Chemical investigation

oral intake, such as calcium chloride, or abnormal losses from the gastrointestinal or urinary tract. The first two of these conditions are usually easily detected, but impairment of the renal function due to congenital anomalies or infections should be diagnosed by appropriate laboratory studies, such as urine culture, intravenous pyelography, blood urea nitrogen determination, etc. Hyperventilation due to injury of the central nervous system or poisoning may produce hyperchloremia and lowered plasma carbon dioxide with a urine in the alkaline or slightly acid range. The serum pH, however, will be elevated.

Prognosis: The prognosis depends on the extent of irreversible renal damage and the proper management. The ultimate prognosis often is better in the more severely affected cases, because they are diagnosed early and treatment is begun before irreparable changes have been established.

Treatment: The aim of therapy is to correct the acidosis in order to prevent further mobilization, renal filtration, and distal tubular deposition of calcium and to replace the continued urinary loss of fixed base. This can be achieved by administration of alkali. A 10 per cent sodium citrate with 6 per cent citric acid solution is more commonly used than bicarbonate or lactate. The amount of alkali and the duration of therapy vary with every patient. Normal weight gain and almost complete correction of the acidosis should be achieved. The need for alkali often changes spontaneously, especially in infants, but always increases in the event of intercurrent infection, a common occurrence in these subjects.

Biochemical Aspects.—In the normal infant and child, and in most adults, diet, growth, metabolism, and intestinal excretion make it necessary for the kidneys to excrete more chloride, phosphate, sulfate, and organic acids than sodium, potassium, calcium, and magnesium, if the composition of the body fluids is to be maintained. Two mechanisms are provided by the renal tubular cells to accomplish this purpose. Both of these mechanisms, the hydrogen ion exchange mechanism and ammonium production, are interrelated. The conservation of base in the urine may be expressed as titratable acidity plus ammonium minus bicarbonate in the urine.[32] In the cases just presented we believe that there is, for an unknown reason, a diminished ability of the renal tubular cells to furnish hydrogen ions in exchange for sodium, potassium, calcium, and magnesium and to permit any large production of ammonium ions. Latner and Burnard[11] have postulated a primary defect of reabsorption of bicarbonate in the proximal renal tubule. This view has been challenged by Smith and Schreiner.[31] At present the exact mechanism is still unknown. This defect in the conservation of basic minerals by the renal tubules can be demonstrated graphically by plotting the sum of the major factors in base conservation (titratable acidity and ammonium) in the urine against the plasma carbon dioxide content (Fig. 1). The regression line, obtained from data for normal and even young premature infants,[11, 33] indicates that as the plasma carbon dioxide falls in a metabolic acidosis, the amount of base conservation per unit of time and per unit of surface area should increase. As seen in Fig. 1, the determinations for Latner's,[11] Smith's,[31] and our patients all fall below the line showing the insufficient production of hydrogen ions and ammonia.

SUMMARY

Two cases of idiopathic hyperchloremic renal acidosis are presented. One was diagnosed when the patient was 8 weeks of age by chemical investigation of persistent acidosis. Appropriate treatment, consisting of the addition of sodium citrate to his dietary intake for 20 months, resulted in apparently complete recovery. The other case was diagnosed when the child was 5½ years of age, when renal calcifications were radiographically visualized. Continued alkali therapy corrected the acidosis and had a favorable effect on the physical development of this patient.

The natural course of this disease is presented. The disturbance of the electrolyte metabolism is described, with emphasis on its importance in early detection of this disease and on the elimination of other illnesses which clinically may simulate this condition.

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PSEUDOTUMOR CEREBRI

Benign Intracranial Hypertension

Jerome E. Maisel, M.D.,* and Joseph Caplan, M.D.**
Hewlett, N. Y.

PSEUDOTUMOR CEREBRI is a syndrome characterized by (1) increased intracranial pressure, (2) a normal ventricular system, and (3) a normal spinal fluid except for pressure. Its clinical features resemble those of an intracranial space-occupying mass, but no mass can be demonstrated by ventriculography, encephalography, arteriography, or surgical exploration.

The purpose of this paper is to present 6 cases of this syndrome occurring in children and to discuss the etiology, symptomatology, treatment, and prognosis.

REVIEW OF LITERATURE

Pseudotumor cerebri was clearly defined as a precise syndrome by Davidoff and Dyke[1] and Dandy,[2] based on the cardinal radiologic feature of a normal ventricular system under increased pressure. It had previously been referred to in the literature as serous meningitis,[1, 4, 5, 6] pseudoabscess,[3] otitic hydrocephalus,[4] or intracranial pressure without brain tumor.[2, 5, 8]

Many authors have attempted to implicate dural sinus thrombosis as the main etiological cause of this syndrome.[4, 9] Ray and associates[10] initially supported this thesis using dural sinusography as a diagnostic technique. However, reporting on 28 cases at the Harvey Cushing Society in 1955, Ray was able to demonstrate evidence of thrombosis in only 10 of the 20 sinograms. He concluded that there were obviously a high percentage of cases in which dural sinus thrombosis could not be held responsible.

Foley[12] gathered 106 cases from the literature and reviewed 60 cases at his own hospital. He suggested that the term "benign intracranial hypertension" be used to describe those cases of pseudotumor cerebri in whom no antecedent trauma, infection, or dural sinus thrombosis is found.

Except for the recent article by Moore,[13] there has been scant reporting in the pediatric journals. This may be partially explained by the fact that this syndrome occurs most frequently in the second and fourth decade of life.

CASE REPORTS

Case 1.—B. F., a 6½-year-old white boy, was admitted to Mount Sinai Hospital in New York City on Nov. 29, 1954, because of headache, ataxia, and vomiting. Some clumsiness and incoordination were noted during the 6 weeks prior to admission. These symptoms had become considerably worse 2 days prior to admission. He was

*From the Department of Pediatrics of The Long Island Jewish Hospital, New Hyde Park, New York, and State University of New York Downstate Medical Center, Brooklyn, N. Y.

**St. Joseph's Hospital, Far Rockaway, N. Y.

unable to sit in a chair unsupported, began vomiting, and complained of headache.

Physical examination revealed a well-developed, well-nourished, alert lad, in no acute distress. Blood pressure was 110/70 mm. Hg. Respiration, pulse, and temperature were normal. There was a moderate degree of generalized hypotonia and weakness. The deep tendon reflexes were normal. There were no pathologic reflexes. He demonstrated an unsteady, staggering gait and past pointing with the upper extremities. The examination of both fundi were normal, although several observers felt that some papilledema was present.

The neuroskull roentgenograms, electroencephalogram, pneumoencephalogram, and ventriculogram were normal. A red and white blood cell count, urine analysis, and complement fixation tests for mumps, eastern equine encephalitis, and Japanese type B encephalitis were normal. The spinal fluid examination was normal.

Bilateral frontal burr holes were made under general anesthesia. On the left side the brain came right to the dura. On the right side a good deal of subarachnoid fluid was present, which emptied forcefully through the incision.

The patient was discharged 6 days after admission. The headache and vomiting stopped and the weakness and ataxia decreased. It should be emphasized that throughout the entire illness he was never uncomfortable or in any acute distress.

The patient developed bilateral epidemic parotitis one day after discharge. This subsided without complication. Two weeks after discharge he was asymptomatic and had a normal physical and neurological examination. He is currently in good health and shows no neurological sequelae.

CASE 2.—R. R., a 10-year-old white girl, was admitted to the Long Island Jewish Hospital, New Hyde Park, New York, on March 12, 1955, because of a suspected intracranial space-occupying mass following trauma. Ten days prior to admission the patient had fallen down a flight of stairs and traumatized the right side of her head. She had been dazed but not unconscious and began to vomit approximately one hour after her injury. She vomited often during the next 2 to 3 days and complained of vertigo. Following the accident she became irritable, apathetic, and complained of recurrent dizziness and headaches. On the day of admission she was quite alert and did not vomit. She complained of pain in the left ear. There was no history of any recent infection or illness.

Physical examination revealed a very cooperative, alert girl. Her temperature, pulse, and respiration were normal and her blood pressure was 120/70 mm. Hg. There was a large fluctuant subcuticular swelling in the right temporoparietal region of the skull. Slight nuchal resistance was present and there was a questionably positive Kernig sign. There were no gross weaknesses. The deep tendon reflexes were more active in the lower limbs than in the upper. No abnormal reflexes were present. The right pupil was slightly larger than the left but reacted equally to light and accommodation. There were slight nystagmoid jerks on extreme lateral gaze which were unsustained. Bilateral papilledema was present and fresh hemorrhages were noted at the periphery of the discs. The veins were engorged.

A total white and red cell count, urine analysis, Schick and Mantoux tests, and skull x-rays were normal. Several pre- and postoperative lumbar punctures yielded normal spinal fluid which was sterile. At the first lumbar puncture, spinal fluid pressure was 500 mm. of water. The spinal fluid pressure subsequently became lowered to 160 mm. of water.

Because of recurrent intermittent drowsiness, bilateral burr holes were placed 24 hours after admission. This disclosed an excessive accumulation of

clear colorless spinal fluid in the subarachnoid space over both hemispheres. There was no evidence of a subdural hematoma. The postoperative course was uneventful and the papilledema and hemorrhages were noted to recede.

She was discharged from the hospital March 25, 1955, considerably improved and has remained in good health.

CASE 3.—S. F., a 5½-year-old white boy, was admitted to the Long Island Jewish Hospital on Jan. 22, 1956, because of a casual observation of bilateral papilledema during a routine preschool examination. He had complained intermittently of headaches for 6 months prior to this examination. There had been no vomiting or loss of appetite.

The physical and neurological examinations were completely normal except for the eye findings. The optic discs showed bilateral papilledema in relatively early stages with some exudate but no hemorrhages. Routine studies, including skull roentgenograms and electroencephalograms, were normal. Spinal fluid analysis was normal.

Burr holes were placed in preparation for a ventriculogram. The brain appeared to be under some tension. When the dura was opened an excessive amount of spinal fluid spurted out of the subarachnoid space. It was not possible to tap the right ventricle. However, air was easily injected into the left ventricle and a normal but small ventricular system was outlined. A right myoplastic type of decompression was done at this time, and the postoperative course was uneventful. At lumbar puncture, 4 days following the operation, an initial spinal fluid pressure of 90 mm. of water was found.

One month following admission he was asymptomatic and the eye grounds improved. His behavior was said to have become more relaxed, outgoing, playful, and aggressive. The patient acquired chicken pox in May, 1956. During this time he complained of severe headaches and a bulge was noted at the site of the operation. Five months postoperatively, papilledema disappeared from the right eye and was noted to be diminished in the left.

CASE 4.—M. D., an 8-year-old white girl, was admitted to the Long Island Jewish Hospital on Nov. 16, 1956, because of loss of vision in her left eye of 1½ weeks' duration. Four weeks prior to admission the patient reported an incidental fall, at which time she had struck her head. She had no headache, nausea, loss of appetite, or vomiting.

The physical and neurological condition was normal except for the eyes. Vision in the left eye was 20/200. A 5 degree central scotoma and an enlarged blind spot were noted. There was papilledema obscuring the entire left disc. The macula was obscured by exudates. The vision in her right eye was 20/70. The blind spot was enlarged and the nasal margin of the optic disc was raised.

Following admission, bilateral burr holes were made. When the dura was opened the brain bulged and was under increased pressure. There were repeated unsuccessful attempts to tap each ventricle. A right-sided cerebral angiography was therefore carried out. Both anteroposterior and lateral views were normal. A lumbar puncture, which was then performed, revealed an initial pressure of 350-400 mm. of water. Pneumo-encephalogram, spinal fluid culture and analysis were normal. The skull x-rays were normal. A right-sided myoplastic decompression was done on Nov. 12, 1956. The child did well postoperatively. On the fifth postoperative day, spinal fluid pressure was found to be 170 mm. The fluid was slightly xanthochromic. The spinal fluid analysis was normal, except for a protein of 56 mg. The xanthochromia and elevated spinal fluid protein may have resulted from unsuccessful ventricular taps.

Normal spinal fluid pressure was recorded on the eleventh postoperative day. Two weeks following the operation, the child stated that her sight had improved. Neurological examination was negative and the area of decompression was soft and pulsating. Considerably less swelling and edema about the macula was noted. The electroencephalogram pre- and postoperatively showed diffuse cerebral dysrhythmia. The patient is currently asymptomatic and shows no abnormal eye findings.

CASE 5.—R. F., a 10-year-old white girl, was admitted to the Long Island College Hospital in Brooklyn, N. Y., on July 22, 1952, because of severe headaches, and diplopia of 2 weeks' duration. Blood streaked stools were noted on the day prior to admission.

Physical examination revealed a well-developed, well-nourished girl in no acute distress. Her temperature, pulse, and respiration were normal. Blood pressure was 120/94 mm. Hg. A soft round liver edge was palpable 3 cm. below the costal margin. The tip of the spleen was also palpable. Paresis of the right external rectus muscle was apparent. There were scattered hemorrhages in the periphery of the left fundus, and moderate bilateral papilledema.

The white and red cell counts, erthrocyte sedimentation rate, urine analysis, nose and throat culture, Schick and Mantoux tests (0.1 mg. OT), and spinal fluid analysis were normal. Blood, urea, fasting blood sugar, total serum protein, albumin and globulin, cholesterol and esters and cephalin flocculation tests were normal. The serum bilirubin was 0.63 mg. per cent, alkaline phosphatase was 16 Bodansky units, and Bromsulfalein retention 11 per cent at 45 minutes. Biopsy of the liver showed hemorrhages and fibrosis compatible with subacute yellow atrophy. The electroencephalogram was characterized by diffuse slow activity, 6-8 cycles per second. Roentgenograms of the skull, chest, and abdomen were negative. Spinal fluid analysis was normal.

Except for an occasional mild headache and nausea the patient was generally asymptomatic and in good spirits. The papilledema, however, became more intense and there was a gradual loss of vision. Following a normal ventriculogram, a subtemporal decompression was carried out to protect her vision.

During the weeks that followed, the papilledema subsided, her vision was regained, and the headaches and diplopia disappeared. Six weeks after admission no abnormalities were noted on neurological examination. The patient, however, later developed cirrhosis of the liver and subsequently required splenectomy and a shunt operation.

CASE 6.—S. F., a 6-year-old white boy, was seen 6 weeks following a normal routine examination because of headaches and fatigue of 3 weeks' duration. He was admitted to St. Joseph's Hospital, Far Rockaway, New York, and subsequently transferred to the Neurosurgery Service at the Long Island Jewish Hospital, New Hyde Park, on Jan. 15, 1955.

Partial paresis of both lateral rectus muscles was noted. There was moderate bilateral papilledema. Peripheral visual fields were normal. Laboratory studies including total white and red cell counts, urine analysis, serology test for syphilis, and spinal fluid analysis were normal. X-rays of the skull and chest were normal. The electroencephalogram showed diffuse slow activity. The signs and symptoms were suggestive of an unlocalized brain tumor. However, a diagnosis of chronic serous meningitis was considered more likely and the patient was referred home for observation.

He was readmitted to the hospital 10 days later, on Jan. 25, 1955, because of 4+ papilledema and complete paralysis of the right lateral rectus muscle. Roentgenograms of the skull

at this time revealed slight separation of the occipital suture lines. The electroencephalogram again revealed diffuse slow activity. On Feb. 1, 1955, a normal ventriculogram was obtained. During the following 2 weeks, the papilledema was noted to recede and the paresis of the right rectus muscle improved. On May 24, 1955, no abnormalities were found on neurological and ophthalmological examinations. The patient has now been observed for 2 years and has remained symptom free.

intracranial pressure. Case 3 was, in fact, detected during a routine preschool physical examination.

Laboratory Tests.—Complete blood counts, urine analyses, and the viral complement fixation studies in Case 1 were normal. Spinal fluid characteristics were normal except for pressure. Skull x-rays were all normal except in Case 6 where some suture separation was noted. Ventriculograms were normal and the ventricles were often described as appearing somewhat smaller than usual.

TABLE I

			SYMPTOMS							CLINICAL SIGNS					MISCELLANEOUS				
PATIENT	AGE (YR.)	SEX	HEADACHE	VOMITING	DIPLOPIA	LOSS OF VISION	WEAKNESS	DIZZINESS	DROWSINESS	OCULAR PALSY	PAPILLEDEMA	RETINAL HEMORRHAGE	ATAXIA	INCREASED INTRACRANIAL PRESSURE	ABNORMAL EEG	SUTURE SEPARATION	ANTECEDENT TRAUMA	DURATION OF SYMPTOMS	PERIOD OF OBSERVATION (YEARS)
No. 1	6½	M	x	x			x				+		x	x				9 wk.	2½
No. 2	10	F	x	x				x	x		x	x		x			x	3 wk.	2
No. 3	5½	M	x					x			x			x				5½ mo.	1½
No. 4	8	F				x					x			x	x		x	6 wk.	1½
No. 5	10	F	x		x					x	x	x		x	x			8 wk.	5
No. 6	6	M	x				x			x	x	x		x	x	x		4 wk.	2½

COMMENT

Symptoms and Clinical Signs.—Headache of varying intensity occurred in 5 cases and was the most frequent symptom. Vomiting, diplopia, loss of vision, dizziness, drowsiness, and weakness occurred less frequently. Unilateral or bilateral papilledema was present in 5 cases; retinal hemorrhages were present in 3 cases, and ocular palsy in 2. One patient had ataxia.

The most impressive clinical feature of this syndrome, in children, has been their general well-being throughout the disease, in spite of the increased

Treatment.—The treatment for this syndrome is symptomatic, depending principally on the intensity of the disease. Some patients required subtemporal decompression for relief of headaches and, in others, it was necessary to prevent blindness.

DISCUSSION

The etiological agents of pseudotumor cerebri appear to be as diverse as they are numerous. Foley[12] classifies this syndrome into three main

groups: (1) otitic cases in which dural sinus thrombosis is the probable cause of increased pressure; (2) a larger group in which there is no history of infection or injury, occurring almost exclusively in women, with a peak incidence in the fourth decade; and (3) a smaller group in which the condition follows an infection or mild head injury.

Effective use of antibiotics should prevent the extension of infection from the middle ear or mastoid area to the dural sinuses. One would therefore expect to find that more patients in the pediatric age group would fall into Group 2 and fewer into Group 3.

Cases 1 and 5 had illnesses which may have been coincident or associated with this syndrome. Case 1 developed mumps during his recovery period. His complement fixation test for mumps was negative during his hospital stay. Case 3 showed microscopic, pathologic, and biochemical evidence of subacute yellow atrophy. The onset of symptoms in Cases 2 and 4 followed a head injury.

Foley's report indicates that a slight pleocytosis is not uncommon. However, repeated spinal fluid analysis on our cases failed to show any indication of acute or chronic inflammatory or neoplastic disease.

The most common causes of increased intracranial pressure are: obstruction to the normal circulation or absorption of cerebrospinal fluid, a space-occupying mass, cerebral edema, and right ventricular failure. These may be differentiated with specific medical and neurosurgical diagnostic techniques.

It is difficult, however, to describe a mechanism which can explain the presence of increased intracranial pressure with an undistorted ventricular system. There is evidence that the increased pressure is due to an intracerebral collection of fluid. At operation, the brain tissue appears wet and swollen. It recedes rapidly as the fluid spurts out of the subarachnoid space.

Blindness may appear much earlier in this condition than in those due to cerebral tumor. This may be related to a sudden increased intracerebral pressure.

The diagnosis of pseudotumor cerebri is one made by exclusion. Careful studies and prolonged follow-up observations are necessary to exclude conditions which may pursue a chronic or recurrent course, such as subdural hematomas in unusual locations, subdural cysts, or ependymal tumors.

The prognosis for this disease is excellent. All of our patients recovered without any temporary or permanent sequellae. Zuidema and Cohen[8] noted, in their 20-year follow-up of cases in adults, that after 2 years it was unlikely for a tumor to arise from one of the silent areas of the brain.

SUMMARY

Six cases of pseudotumor cerebri are reported in children. The syndrome is characterized by headache, vomiting, papilledema, and unexplained increased intracranial pressure. The benign nature of this disease is emphasized.

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PEDICULOSIS CAPITIS IN PRESCHOOL AND SCHOOL CHILDREN: CONTROL WITH A SHAMPOO CONTAINING GAMMA BENZENE HEXACHLORIDE

JOHN GARDNER, M.D., F.A.P.H.A.*
LONG BEACH, CALIF.

THE prevalence of pediculosis capitis remains a constant and troublesome problem in most communities, particularly among school children. Kaiser[1] noted that in Rochester, New York, it was the second largest cause of absenteeism during the 1944-1945 school year. Other surveys have found its prevalence among school children to range from less than 1 per cent to over 50 per cent.[2, 3]

Unlike the communicable diseases, the host does not develop an immunity to the ectoparasitic infestations and therefore the spread of pediculosis is not interrupted by the development of immunity in affected individuals. Hence, its control depends solely on enforcement of good hygienic practices and effective measures to rid infested individuals of the parasite.

Measures for eliminating pediculosis infestations should quickly destroy both lice and nits. Ideally, it should also be cosmetically acceptable and simple and safe to use. With such a pediculicide, supervisory problems would be minimized and the success of the program greatly enhanced.

The preparations that are presently available for the eradication of pediculi have several disadvantages. These lessen their acceptability and detract from the success of a control or eradication program. These disadvantages include: a required contact of up to 24 hours or more of the pediculicide to ensure effectiveness, a turbaned towel or other head covering during the medication contact period which can be embarrassing to the patient, unpleasant odors and other cosmetic ineleganee and, with many preparations, a chance of skin irritation or sensitization.

Recently, a preparation was presented to us that offered the prospect of overcoming these disadvantages. This is a shampoo containing, as the active agent, gamma benzene hexachloride, a potent pediculicide and scabicide. In this shampoo,* the gamma benzene hexachloride is solubilized and combined with surface active agents. In vitro studies had demonstrated the shampoo to be capable of destroying nits within a few minutes, presumably because the surface active agent facilitated penetration of the pediculi and their ova.[4]

MATERIAL AND METHOD

Observations were made on 47 children, representing the number found

*Chief, Division Communicable Disease Control, Department of Public Health, Long Beach, Calif.

*Kwell Shampoo, kindly supplied by Reed & Carnrick, Jersey City, N. J.

affected during routine examinations of selected groups of children both by the school nurse and our Public Health Nursing Staff. No Negro patients were included in this group. Of the infested patients, 87.2 per cent were female.

Treatment was applied either by the nurse or by the parent of the child according to the following simple instructions: (1) thoroughly wet the hair with warm water, (2) apply the Kwell Shampoo as with any ordinary shampoo, (3) rub lather in vigorously for a full 4 minutes, being sure to go over the entire hairy area, (4) rinse hair thoroughly, (5) rub vigorously with a dry towel, and (6) if any nit shells remain, remove with a fine tooth comb. The following day, the children returned for re-examination.

RESULTS

In all cases, a single shampooing with the preparation proved effective in completely destroying all evidence of infestation. No live pediculi or nits were observed upon re-examination of these patients one to five days after treatment.

From Table I it can be seen that the shampoo was used in a total of 47 cases with an age distribution of 1 to 49 years. There were 41 cases of scalp infestation alone, 1 case of infestation of scalp and eyelashes, and 5 cases of pubic infestations. In all these cases, all evidence of live pediculi was eliminated after the first treatment. Additional applications of the shampoo were necessary in 8 cases to aid in the removal of residual nit shells. These might have been avoided with more vigorous shampooing technique. In Table II, we have shown the number of patients who have been shampooed one or more times. Of the total group, 39, or 83 per cent, were completely clear after one visit, 5 required a second treatment for removal of nit shells, and 3 required a second and third visit. In all, this represents a total of 58 separate applications.

TABLE II. PATIENTS SHAMPOOED ONE OR MORE TIMES

	NUMBER	PER CENT
One visit	39	83.0
Two visits	5	10.6
Three visits	3	6.4
Total	47	100.0

A noteworthy feature of treatment was the ready acceptance of the procedure, which is no different from a conventional hair shampooing. Both the mothers and nurses found the treatment pleasant and easy to use. No evidence of irritation or other adverse effect was encountered.

TABLE I. AGE DISTRIBUTION AND SITE OF INFESTATIONS

AGE GROUP	TOTAL	SCALP ONLY	SCALP AND EYELASH	PUBIC	PER CENT
1- 4	10	10			21.3
5- 9	15	15			31.9
10-14	5	5			10.6
15-19	8	4	1	3	17.0
20-24	6	5		1	12.8
25-29	1			1	2.1
30-34					
35-39	1	1			2.1
40-44					
45-49	1	1			2.1

DISCUSSION

A treatment for pediculosis that combines "one-shot" effectiveness with a high degree of patient-acceptance affords an opportunity for control of infestation at both the school and family levels. An advantage of the shampoo method of treatment is its simplicity and acceptability to patient and family. The method avoids the onus of previously available treatments that stigmatize the patient.

In Kwell Shampoo, the gamma benzene hexachloride is available in solution form rather than the previously available suspensions. In solution it apparently is much more rapidly effective in its pediculicidal action. In addition, the surfactant not only promotes penetration of the active agent into the parasite, but it also loosens nits from their attachments to the hair. Since safety is also an essential requisite for an acceptable pediculicide it is important to note that gamma benzene hexachloride has demonstrated a remarkable absence of toxic, irritative, or sensitizing effects.[6, 7]

SUMMARY

Forty-seven children affected with pediculosis capitis were treated with a shampoo containing 1 per cent gamma benzene hexachloride.

A single shampooing sufficed to eradicate infestation with pediculi and viable nits in all cases. The effect was achieved in a few minutes, the actual contact period of about 4 minutes and the total procedure taking no more time than an average shampoo.

Nurses and parents who administered the treatment reported it was both simple and pleasant to use, and readily accepted by the patient.

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SUPPURATIVE ORCHITIS DUE TO PSEUDOMONAS AERUGINOSA

E. T. McCartney, M.C., M.B., F.R.C.S., and I. Stewart, M.D.
Keighley, England

THE organism of "blue pus" is the only member of the group Pseudomonas which is pathogenic to man. The others form pigments of various colors and are widely distributed in soil and water. Wilson and Miles[5] summarize the pathogenic effects as follows: ". . . gives rise occasionally to suppurative processes and occasionally to generalised infection. Among the commonest manifestations are middle ear suppuration in children, destructive lesions of the skin, sometimes described as ecthyma gangrenosum, in children and adults, and necrotic and ulcerative lesions of the alimentary mucosa. The respiratory tract, the eye, the joints and the kidneys are sometimes affected. Wounds are often infected. There is also reason to believe that the organism plays a part in some cases of infantile diarrhoea. Infection may be primary or secondary and is often acute and rapidly fatal."

CASE REPORT

A boy, prematurely born and with a birth weight of 5 pounds 1 ounce, was slow to take food and on the tenth day, when his weight had dropped to 4 pounds 7 ounces, began to vomit. A tense tender swelling was found in the right groin. No testicle was felt in the right side of the scrotum. A tentative diagnosis of an obstructed inguinal hernia was made and operation was carried out under nitrous oxide and oxygen anesthesia, reinforced by a local anesthetic. The right inguinal canal was opened and a swollen and engorged testicle was found. No torsion could be demonstrated. The peritoneum was opened at the internal ring. The bowel observed was normal but a small quantity of blood-stained viscid fluid oozed out. The testis and cord were excised.

Fig. 1.—The abscess is seen to the left and the body of the testis to the right.

Two days after operation the child had a brief attack of diarrhea and recovered spontaneously in about 24

From the Victoria Hospital, Keighley, England.

hours. Otherwise convalescence was uneventful.

Pathology and Bacteriology.—The cut surface of the body of the testis showed a crescent-shaped zone of bluish green pus lying posteriorly and extending to both poles, its center being 1 cm. thick. In its concavity lay the body of the testis, lobulated on its posterior margin, the line of junction showing a thin zone of hemorrhage.

Histological section showed the purulent zone to be a solid mass of polymorphonuclear leukocytes. The body of the testis showed tubules in the embryonic state with occasional patency. The hemorrhagic zone was partly of fibrin in contact with the pus and partly of granulation tissue in contact with the tubules. The abscess was completely within the tunica albuginea.

Cultures from the viscid peritoneal fluid and from the abscess each gave a pure growth of *Ps. aeruginosa*. Culture of the stools during the bout of diarrhea gave a predominant growth of the same organism.

DISCUSSION

With the assistance of the librarian of a large reference library, we have been able to discover only one similar case in the literature. Longhi[3] describes a boy of 12 years of age who was admitted to a hospital with a history of testicular swelling for 4 weeks. When examined the swelling was the size of a hen's egg and adhered to the scrotal wall. No distinction could be made between the epididymis and the testis. The patient was in high fever and suffering great pain. There was no urethral discharge and no involvement of the prostate or vesiculae.

Treatment with penicillin was ineffective. The scrotal skin reddened and broke down extruding a fungating mass. Cultures of the initial discharge gave a pure growth of *Ps. aeruginosa*. Pain steadily diminished. Bismuth salicylate was then employed without effect and then streptomycin; finally sulfadiazine was given for a month. Meantime the mass steadily diminished to form a dense scar.

Wassermann and Kahn reactions were negative. Films of the discharge were negative for tubercle bacillus and guinea pig inoculation of the discharge gave no reaction. Dark ground examination of the discharge showed no treponemata and films of the urethral secretion and discharged showed no gonococci. *Ps. aeruginosa* was recovered repeatedly from the discharge and also from the urine.

Agglutination reactions between the patient's serum and suspensions of the infecting organism showed agglutination to $\frac{1}{128}$ whereas controls showed agglutination to $\frac{1}{4}$. Injection of killed suspension into controls gave no reaction but provoked a violent reaction in the patient.

Histological section of the lesion showed nonspecific granulation tissue with numerous gram-negative rod-shaped organisms. No evidence of syphilis or tuberculosis was found, although for a considerable time the lesion was believed to be a specific granuloma.

There seems no doubt at all that Longhi's case was a primary infection by *Ps. aeruginosa* and the appearance of the organism in the urine indicates a transient bacteremia just as, in our case, the presence of the organism in the abscess, peritoneal discharge, and stools, is presumptive evidence of bacteremia.

According to Kerby,[2] bacteremia in children is a rare disorder and he was only able to accept 39 cases in the

literature. Geppert and others[1] claimed that infections had become more frequent and of graver character as a result of the widespread and indiscriminate use of antibiotics and describe 8 cases of destructive lesions of the skin, bowel, and respiratory tract in which 3 patients died. In our case there was no record of the mother having received antibiotics.

The source of the infection in our case was not known. It may have originated in the umbilical cord or have been acquired by ingestion. According to Oeklitz and Schmidt,[4] the organism may even be present in the intestine of the fetus before birth. The stage of the granulation tissue was consistent with infection having occurred at about the time of birth.

SUMMARY

A case of suppurative orchitis due to *Ps. aeruginosa* in a child of 10 days of age is described in which there was presumptive evidence of bacteremia. Operative excision was followed by recovery.

We are indebted to Mr. Adrian Wilson for the photograph.

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BRITISH-AMERICAN PEDIATRICS AND CHILD CARE; GENERAL PRACTITIONERS, CONSULTING AND PRACTICING PEDIATRICIANS; PEDIATRIC EDUCATION

LÆTITIA M. BRUCE, M.B., CH.B., AND WILBURT C. DAVISON, M.D.
DURHAM, N. C.

UNTIL 1911, when the Lloyd George medical panel law was enacted in England, British and American pediatric practice and child care were quite similar.[1] There were very few pediatricians in either country, and they were solo consultants connected with charity hospitals, who also saw private pediatric patients referred to them by general practitioners for diagnosis and advice. The treatment usually was carried out by the general practitioners, and only rarely by the pediatricians. None of the British or American pediatricians of this pre-1911 era accepted children for continuous routine care and supervision which was provided, if at all, by the general practitioners and Health, Welfare and District Nurses and Visitors, Child Health Officers, Health and Welfare Centers,[2] School Clinics,[3] nurses qualified as midwives (SCM), and later by the home care, premature nurses, such as those trained by Dr. V. Mary Crosse[4] in Birmingham. As a matter of fact, mothers, general practitioners, and consulting pediatricians did not consider routine child care necessary. Some still are of that opinion.

The private consultation work of this period developed because general practitioners referred children to pediatricians for the chief and often the only reason that they were children and growing, developing human beings with their own specific problems[5, 6] which were difficult to understand, and not micro-adults[5] or miniature men or women, just as every physician now refers dogs to veterinarians because they are different animals. Later, consultations changed to a "disease" basis—thus a general practitioner would refer children to a pediatrician with a special knowledge of diabetes, epilepsy, cardiac disease, etc.,[7] a custom which many of us deplore, because pediatrics is the last stronghold of the general point of view in medicine.[8] Other specialties, and even general practice, have their splinter subspecialties.

EVOLUTION OF AMERICAN PEDIATRICS

About 1911, some American consulting pediatricians began to provide routine care for children, like that of general practitioners, as a *secondary* activity, in addition to their consultation practice, e.g., Fife and Sinclair in Philadelphia, and Saunders, Zahorsky, and Tuttle in St. Louis, among others.[7] This trend was gradually rising before World War I, but spread more widely after it. Perhaps part of the impetus was the experience with French puericulture gained by the

From the Department of Pediatrics, Duke University Medical Center.

younger consulting pediatricians sent to France during World War I by the American Red Cross to help with the care of the French War Orphans. Several other factors are also responsible for this change in American pediatrics from solo consultations to child-care practice. For example, some consulting pediatricians recognized the need, demand, and market for systematic, periodic supervised child care and made this field their *primary* occupation, rather than a side line. J. H. Mason Knox was one of the leaders in changing pediatrics from the diagnosis of the diseases and the care of sick children to what we know now as child care. He let it be known, early in his years of practice, that he would be glad to see well children for general health supervision. The idea of inviting visits from healthy children and charging for them was then so unorthodox as to be considered unethical, and the legend persists that there was outspoken professional sentiment against it.[9] Lucas in San Francisco, Royster in Norfolk, and others commenced seeing children from birth to the age of 2 or 3 years at frequent intervals, with advice to the mothers about feeding habits, growth, development, inoculations, and so forth, sometimes for a monthly or annual fee.

"Well-baby" conferences were started before World War I and the "summer round-up" for children entering school was soon extended throughout the entire period of childhood.[9a] The pediatricians early recognized that the environment is a potent influence on the life and welfare of the individual and they sought those elements in the environment which could be modified favorably, e.g., milk supply, school desks and lighting, poison sources, causes of accidents, etc., in order to avoid placing the individual at a disadvantage so far as health was concerned.[9b]

This trend has been so marked that the erroneous view sometimes is expressed that the practicing pediatrician is the only person who can give the child the professional care and advice he needs in sickness and in health as he travels the confusing path of growth and unfolding personality, on the ground that only a pediatrician knows children from birth throughout adolescence, and his concept of his responsibilities has broadened to include emotional and social reactions. Moreover, because of the intimate relationship of the practicing pediatrician with the parents, he has become in many instances quite logically the family health counselor. As a result, the United States may soon have a new type of family doctor, who does everything except obstetrics. Such doctors usually do not treat the adults in the family but know sufficient medicine to refer them to general practitioners or specialists. Because of their pediatric training in preventive medicine, they also are among the most active leaders in community health and school responsibilities.[6] Many who are expert in ministering to adults are rarely by interest, training, or temperament adept in handling the problems of childhood.[6] Some American mothers say that the difference between visits by a general practitioner and a pediatrician is that the former examines only the complaint area and is solely interested in ill patients while a pediatrician studies the whole child and wants to keep him healthy. Another

American argument in favor of child care by a practicing pediatrician is that by having a smaller field he probably has a wider knowledge of children than the family physician who must keep up with the care of patients from birth to old age. If a child has a complicated illness, however, the practicing pediatrician refers the patient to a hospital, because diagnostic facilities are available there. In Britain the same sequence holds, except that it is not a specialist who sees the child in the first instance, but the family doctor.

This movement snowballed before the pediatric academicians recognized it and shifted the type of training to meet the demand. For example, in 1926 Lucas wrote to one of us, living in the Hopkins ivory tower, for a pediatric resident to share his growing load of routine child care. The resident who accepted this appointment, like all residents of his generation, had been trained to diagnose and treat the ills of children, and was frustrated by seeing the same well children every month or two. Some pediatric departments still ignore the need for training in routine child care. The demand for this service continued, however, and the number of pediatricians mushroomed.

Very soon, the American mothers realized the benefit of this complete, continuing, comprehensive, and total child care, health supervision, and psychological, social, and vocational rehabilitation.[9c] They are so convinced of the value of well-baby care that attempts to discontinue such appointments during the wartime shortage of doctors led immediately to such pressure that they had to be resumed. Many mothers displayed ingenuity or adopted the subterfuge of having a "sick baby" to obtain appointments. Once in the doctor's office, they managed to obtain a "well-baby checkup." Although well-baby care is now part of the American way of life, well-child care is being neglected. Only 14 per cent of the patients in the average pediatrician's practice are over 6 years of age.[9d]

Another factor in this trend from general practice is the American Specialty Boards, which were originally established to protect the public against self-acclaimed and often untrained specialists, but which have now acquired such prestige and have become so attractive, especially to recent graduates, that they have done more harm than good by depleting the supply of general practitioners, and by making the specialists and the public believe that specialists are exalted beings, a cult largely started by the surgeons though the other specialties are becoming increasingly guilty. As a result, many mothers believe that only a specialist is reliable and they lose confidence in their family doctor because he is not a specialist, and transfer to a practicing pediatrician, mainly because he is a specialist.[10]

The American general practitioners, on the other hand, either did not recognize this development or were not interested in it. They actually hastened the transition of routine child care from the family doctor to the practicing pediatrician, because some of them, British as well as American, are not fond of babies, and in fact are sometimes afraid of them. Lack of experience in a subject causes dislike of that subject. Some family doctors

feel insecure in giving routine child care because they have been too busy to follow the pediatric literature. In those cases, the general practitioners or obstetricians suggest to the expectant mother that she engage a practicing pediatrician. Even without being referred by physicians, many women make such arrangements on the advice of other mothers, particularly those who have read the lay medical journals, e.g., *Time* and the *Reader's Digest*. This movement also was given impetus by the White House Conferences on Child Health, especially by President Hoover's 1931 Children's Charter* and by the Emergency Maternal and Infancy Care (EMIC) program established by the U.S. Children's Bureau in 1943 during World War II. Before EMIC, many parents did now know that a pediatrician was not a foot doctor.[6]

Another factor in increasing the number of pediatricians at the expense of the general practitioners, which has not been sufficiently emphasized, is that after the Second World and Korean Wars, the United States gave every military physician sufficient money to return to hospitals and medical schools for retraining. Practically all of them used this "GI money" to become specialists. For example, 40 per cent of the Duke graduates before the war entered general practice and within five years after the war only 7.7 per cent.

As a result of some or all of these factors, American pediatries, at present, consists of a few consulting pediatricians attached to hospitals and university clinics as members of a consulting team, usually on full-time salaries as in Britain, and a rapidly growing number of practicing pediatricians who, with rare exceptions, specialize in the care of children up to a certain age, and whose major activity is the maintenance of child health and the prevention of diseases.[11] Almost every community of 15,000 or over in the United States now has a pediatrician. In North Carolina, the number of pediatricians has grown from 11 to 131 in twenty-five years; some towns in which a pediatrician could not make a living a few years ago now have four child-health practitioners who are so busy that they have asked Duke University Medical Center for one or two more. The number of these new practicing pediatricians in the United States has grown to the present 5,981, who have been certified by the American Board of Pediatries.[12] Of the 218,061 American medical school graduates, 6,567 limit themselves to pediatries and 2,156 practice part-time p e d i a t r i e s—a total of 8,723.[13] To bring this large group together, the American Academy of pediatries was organized in 1930, and now has around 4,500 members in the United States.[13] In 1946-1947, 11 per cent of American children received medical care exclusively from pediatricians.[6] In 1948, the health care of 50 per cent of American children was fully or partially supervised by pediatricians in private offices, clinics, or through social agencies. Now the percentage is approximately 65.[13]

Actually, but unfortunately, in addition to the original British-American consulting pediatrician attached to a

*President Hoover's White House Conference on Child Health ond Protection, "recognizing the rights of the child as the first rights of citizenship," pledged itself "to prenatal, natal and postnatal care, health protection from birth through adolescence, and periodical health examinations, for every child, regardless of race, color or situation, wherever he may live under the protection of the American flag."

teaching clinic or hospital, and the practicing pediatrician who is a child-care specialist and family counselor, a third variety of pediatrician has arisen with a huge office, innumerable cubicles, dozens of nurses and secretaries. He provides excellent child care but on a completely impersonal, commercial, and "production line" basis. Many of them purposely build their examining cubicles so small that the mothers cannot get in and delay the procedures by asking questions. They later give these mothers an opportunity for brief questions, with or without a fee, by setting aside certain hours during the day for telephone calls. This is carrying efficiency too far, and taking all of the humanity out of pediatrics. Perhaps the mothers eventually will resent this treatment and return to general practitioners for the health care of their children.

CHILD CARE BY GENERAL PRACTITIONERS

It is physically, numerically, and financially impossible for the supply of practicing pediatricians, large though it seems in this country, to provide child care for all of the present forty-seven million children scattered throughout the United States—over 5,000 children per pediatrician. With four million American babies being born each year,[14] the child health problem is growing faster than the rapid increase of pediatricians. Furthermore, in spite of the rise of pediatrics, many American parents still desire a family doctor, or family health coordinator. Unfortunately, from the end of World War II to the present, the number of general practitioners has been depleted by death with very few young replacements. Fortunately, however, among the most recent American graduates, the percentage going into general practice is increasing, possibly because the specialties are becoming crowded. It is hoped that these youngsters will practice pediatrics and geriatrics. There is no reason, in spite of previous quotations to the contrary, why a family doctor cannot supply routine care of children, as well as of adults. There are still 60,000 American general practitioners with a genuine interest in children,[15] a quality which is essential to good child care. Some of these family doctors had been graduated prior to 1930, when there was limited pediatric training in medical schools or in internships, but they have kept up with the growing mass of pediatric material, and have attended postgraduate courses in the new and preventive aspects of child care, such as that at the Southern Pediatric Seminar at Saluda, N. C., and those organized by the American Academies of General Practice and Pediatrics, and the Harvard, Washington, Duke, and other medical schools.

The general practitioners who have been trained since 1930 have had better, but still inadequate, medical school and hospital instruction in pediatrics, but many of them have continued their pediatric interest through refresher courses. There is no need for pediatricians in the localities in which these family doctors practice because they do everything a pediatrician can do. In many instances they do a better job of child care because they treat all members of the family. These localities are slowly increasing, thanks to better pediatric instruction in medical schools, more time

allotted to the children's outpatient departments and well-baby clinics in rotating internships, and, last but not least, the excellent postgraduate programs. Instead of the usual query: "Is the general practitioner doomed?"[11, 16] some believe that the pediatricians in the United States are destined to be crowded out by the general practitioners who like children and who have kept up to date.[17]

STATUS OF BRITISH PEDIATRICS

Most members of the British medical profession still believe that child care should be only in the hands of the general practitioners and that pediatricians should only be consultants attached to hospitals. The prevailing British view of child care has been summarized by the late Sir James Spence[3]: "First and foremost it would become fully accepted that the intelligent care of children requires one doctor for the whole family —requires in fact a family doctor. This leads us naturally to reject the view, which is growing in the U.S., that the home care of children should be in the hands of separate paediatric practitioners. We feel that such a development would not be in the best interests of family life and domiciliary practice in Britain."

When the National Health Act was passed, British private pediatric consultation practice almost disappeared, and the British pediatricians usually see only the patients referred to the hospitals to which they are attached. Some British pediatricians, however, still have private practice in addition to their salaried National Health appointments, and they are consulted by the family doctor and the parents in case of difficulty.[18] The British pediatrician's private practice is a part-time occupation, is mostly consultant, and involves much less day-to-day doctoring of individual children, much less telephoning, little night work, and little care of healthy children.[18] In most British towns it is difficult for a pediatrician to make a living solely from private pediatrics,[18] in contrast to the American practicing pediatrician, who makes a reasonably comfortable income.

Everyone in Britain is entitled to free care under the National Health Service, but there are still some mothers who do not like sitting in hospital waiting rooms, and can afford not to; others who want to be sure they will see the pediatrician and not one of his junior assistants; and some who desire a more leisurely consultation than they get in a clinic with the doctors working under pressure.* There are also parents whose children suffer from recurrent upper respiratory tract infections, enuresis, and other long-standing problems, and who want special attention. The very worried parents of children who steal or show some other severe and perhaps embarrassing behavior disorder often seek private advice.[18] In addition, there are in Great Britain some mothers, mostly from the United States, who want a pediatrician to follow their babies from birth through adolescence because they cannot distinguish between a British general practitioner who is interested in routine child care and those who have little or no desire to supervise healthy children. If these

*Private Health Insurance, similar to American Blue Cross and Blue Shield plans, to provide medical and nursing expenses for those who prefer private care to the National Health Service, is expanding in Britain at an annual rate of 30,000 new subscribers.[19]

mothers inquire of the British consulting pediatrician who is always attached to a hospital, however, they are usually referred to a general practitioner who is known to be interested in children, and, once they understand the arrangement, these American mothers seem to like it very much. This doctor also will look after the whole family and will certainly consult the hospital pediatrician if he is worried. There is, of course, the other side of the problem: British mothers in the United States. For example, a very intelligent English woman who married and went to Chicago found it difficult to get the help she needed. When the whole family was ill she had trouble in finding a family doctor to visit her sick child as well as the other members of the family.[20]

Another important difference between British and American medicine, and no one knows which is preferable, is the strictly limited British opportunity for specialization; a pediatrician, no matter how well trained, cannot, or at any rate does not, set himself up as a pediatric consultant until there is a hospital vacancy. His only alternative under the National Health Service is to become an assistant to some established general practitioner on a one- or two-year contract without any assurance of being made a partner. Perhaps if additional financial efficiency awards were given to trained pediatricians who are in general practice, the discontent of these men would be reduced and the general care of well and sick children in Britain would be improved. These doctors could devote their time chiefly to the care of children but also be available for diseases in the older age groups so that they would in effect be family doctors with a special knowledge of children. The "unemployed registrar" problem may in this way be a source of strength in the future if it is handled sympathetically from the financial point of view. Apart from combining the advantages of the family doctor with a better knowledge of child-health care, the educational value of such people spread throughout the community cannot be ignored.[21] It also would be interesting for some enterprising British pediatrician to try the American type of private child-care practice without any subsidy of salary from the government.

The status of a British general practitioner also is "frozen,"[22] a situation which has grown worse since the British nationalized their health services in 1948. A family doctor who acquires training as a specialist must wait for someone to die and vacate one of the limited number of hospital appointments so that he and many others can apply.

DISCUSSION

Both in Britain and in the United States, the responsibility for child care should be in the hands of one individual, the family doctor in Britain and the general practitioner *or* practicing pediatrician in this country. The chief argument for child care by the practicing pediatrician is that he can provide complete care himself, while the general practitioner is hampered, as Spence[3] recognized, because "a great number of authorities, institutions, agencies, societies and professions share in arranging the health and welfare of children. There are so many of these agencies that

they often are at a loss to know how to bring their aids and encouragements at the right time to the families which need them." Under the British program, "the child-welfare center remains the chief agency for advising mothers about the care and feeding of their children in health.[3] Some of the mothers also go to the center for advice on minor illnesses in their children. An analysis of attendances at welfare centers showed, however, that "one third of the infants did not attend; one third attended occasionally; and only one third attended regularly for all or some part of the year."[3]

Most Americans believe that a compromise between the British and American systems is preferable to either extreme, i.e., child care should be in the hands of general practitioners if, and only if, they have an interest in and knowledge of child care, but that if no such family doctor is available, child care should be in the hands of practicing pediatricians trained to provide this skill, and that under this "complementary" program, the health of children is better and the morbidity and mortality rates are lower.

PEDIATRIC EDUCATION

The most important factor in British, American, or any other system of child care is the adequate training of general practitioners, and appreciation by students of the value to the community of well-trained and interested family doctors. In spite of the trend in America toward greater numbers of practicing pediatricians, much child care, in the United States as well as in Britain, as previously mentioned, must still be provided by family doctors; therefore the medical schools must increase their efforts to provide them with a sound training in this field. In order that medical school faculties and hospital staffs may furnish adequate undergraduate and postgraduate training so that general practitioners and practicing pediatricians can supply the best type of child care, they should be alert to the best interests of children and to the desires of the mothers. The task is easier if these interests and desires coincide, as they usually do. For example, mothers have always wanted to room with their hospitalized children, and we are just now learning that rooming-in is beneficial for ill children[3] as well as for the newborn,[23] and that our former strict visiting rules and nurseries for the newborn[24] are harmful.

Most teachers of pediatrics are agreed that all medical students should have some experience, preferably early in their course, with children and families in a normal environment, namely, their homes. This experience was lost when "outside obstetrics" was abandoned.[25] Some medical schools are assigning students to families as advisors, and others, with the help of the British College of General Practitioners[26] and the American Academy of General Practice, are stimulating interest in family practice and child-family relationships by preceptorships with outstanding general practitioners.[6, 27] A few schools are experimenting with courses in General Practice.[28] The chief aim of an undergraduate pediatric teaching program should be to "sell" child care, i.e., to simplify the subject so that students will like infants and children instead of being confused by being crammed with data

about growth, development, numerous infant feeding mixtures, and rare diseases. They should be taught to recognize the more common illnesses in the outpatient department rather than listen to learned discussions on the usual collection of rarities in the pediatric wards, which are of such great interest to the professors. The pediatric curriculum must also provide training in preventive pediatrics and routine child care.

In Britain, although several university pediatric chairs carry the title of Professor of Child Health, and some of the consulting pediatricians have diplomas in Child Health (D.C.H.), the emphasis in pediatric graduate training (residencies and registrarships) is entirely on pediatrics as a consultative specialty. In the United States, although the first pediatric department for the prevention of disease was established in 1914 in Philadelphia by the late Howard Childs Carpenter, who devoted most of his life and efforts to the development of child-health care,[29] much of the pediatric graduate training (residencies) also is in diagnosis and treatment. Some American practicing pediatricians are still frustrated, discontented, and intellectually bored,[6, 30] because as residents they saw only the interesting clinical material and rare cases in the wards of a large hospital and are now dissatisfied by not seeing similar patients in their practice. To remedy this situation, which was first recognized in 1926, as previously mentioned, the Duke pediatric residency, which was started in 1930, emphasized outpatient, well-baby, and school-clinic experience. Few American pediatric exresidents are dissatisfied with the type of practice they are having, which is 75 per cent preventive pediatrics, if their residencies have stressed outpatient teaching,[31] well-baby, school, and special clinics, affiliation with neighboring special and general hospitals, training schools for retarded children,[6] and, last but not least, home care preceptorships and pediatric office apprenticeships,[26, 27] even if only for a week or two. House visits enable the general or pediatric practitioner to perform better his increasingly exacting duty of child guidance. In the home he can tell whether the mother is a neat and orderly perfectionist (perish the thought!); or whether she is so sloppy as to pile an electric hotplate on a 'phone book by the baby's bed to boil some water when he has croup (perish the baby!) or whether daddy reads the paper or watches television while the doctor examines his sick child; or, per contra, whether daddy is the bossy, interfering type. This a pediatric consultant cannot do.[32] Too often pediatric hospital training has equipped the residents only for the care of seriously sick infants and children—"that vitally important 10 per cent"—and for certain types of research, but not for the care of the run-of-the-mill well babies, nor of those with sniffly noses, bronchitis, "strep" throat, otitis, diarrhea, measles, eczema, "colic," etc., who should never see the inside of a hospital, and who comprise the great majority of private patients.[32]

The training of two types of American pediatricians has also been suggested: (1) a practicing pediatrician whose interest and emphasis in life are centered on the routine care of children, and who is trained primarily in

the physical, emotional, and psychological aspects of preventive pediatrics so that he can recognize and treat minor physical and mental illnesses which constitute the bulk of pediatric practice, and (2) subspecialists or superspecialists, with their focus on an organ, e.g., the heart, or on special conditions, such as allergy, dermatology, hematology, pediatrics of the neonatal period, neurology, etc., and who are primarily interested in the more rare or unusual conditions.[33]

Perhaps the most neglected field of pediatric education is that of refresher courses for general practitioners. As Spence[3] has shown, the difficulties and uncertainties about the nature and type of acute illness in infancy demand from the family doctor a high level of diagnostic skill and therapeutic experience for which he requires special undergraduate and postgraduate training and without which the quality of medical care will be inadequate. The advance of knowledge about disease in childhood has been so rapid in recent years, and is continuing at such a rate, that regular postgraduate teaching of family doctors has become a great responsibility of the universities.[3] Unfortunately, some of the medical school pediatric faculties do not know the type of postgraduate training which a general practitioner needs or desires. Equally important is the failure of some family doctors to realize that they need refresher courses. However, the British College of General Practitioners[26] and the American Academy of General Practice are cooperating with the medical schools and teaching hospitals so that the content of the postgraduate training is more nearly meeting the situation.

Both British and American medical educators must also solve the following problems: (1) how to teach undergraduate medical students and postgraduate physicians so that they can provide better child care as general practitioners or pediatricians; (2) how to maintain the present progress[34]; (3) how to lower the mortality and morbidity rates even further, especially for accidents[35] and poisoning[36] (the highest causes of childhood deaths), cancer and leukemia[37] (the second commonest causes), and conditions among infants in the first month of life (the perinatal mortality is 43 for 1,000 live births,[38] and even in the better hospitals has not been reduced for the past seven years[39]), and (4) how to educate children so that child delinquency and later neuropsychiatric breakdowns can be avoided.

CONCLUSIONS

Family doctors and practicing pediatricians must "coexist" and work together for the benefit of child health. Both groups are necessary and equally important. British and American medical schools and hospitals must train both groups so that the job gets done by providing better and less boring courses in child care, and demonstrating their value to undergraduate medical students and interns, and also by organizing more and better refresher courses for general practitioners who desire to keep up with the advances in this field. Radical measures are needed to afford more experience for interns who plan to go into general practice.[6] Pediatric residencies must shift their emphasis from the rare and difficult diagnostic inpatient problems to the run-of-the-mine outpatients.

Obviously teamwork is essential for this comprehensive and continuing care. Physicians, nurses, psychologists, psychiatrists, dietitians, occupational and physical therapists, students of medicine and nursing, schoolteachers, scout leaders, and, last but not least, social workers all must unite and accept the total and continuing responsibility for the health of the individual or the family as a unit in order to safeguard children from conception through adolescence. All of these workers must be interested in the child as an individual with personal, family, and environmental problems.

Equally obviously, any team, athletic or medical, needs a captain, and he or she should not be selected because of having an M.D., Ph.D. in Psychology, or M.S. in Nursing, but rather on the basis of having an instinctive love and understanding of children, and an ability, like that of Osler, to make each patient feel that everyone on the team is primarily interested in his or her welfare.[40]

The most important factors are (1) the education of nurses, physicians, and the public in the need for this total care and in the value of teamwork,[40] and (2) a definite plan of continuing and progressive supervision in which the patient, the family, and the team participate.

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Clinical Pathological Conference

THE CHILDREN'S MEDICAL CENTER
BOSTON, MASS.

SIDNEY FARBER, EDITOR
JOHN M. CRAIG, ASSISTANT EDITOR

CLINICAL HISTORY

THIS was the first Children's Medical Center admission of this 6-day-old white male infant, with the chief complaint, since birth, of cyanosis on crying. The patient was the result of the first pregnancy of a healthy 24-year-old woman. The pregnancy and delivery were completely normal. The child breathed and cried spontaneously, but duskiness was noted immediately. The birth weight was 8 pounds 2 ounces. While in the newborn nursery the child continued to appear dusky, and the lips, hands, and feet were cyanotic when he cried. The baby did well in the nursery and the cyanosis decreased in intensity. An electrocardiogram was done; this was abnormal and the child was sent to The Children's Medical Center for further evaluation.

The family history was noncontributory.

On admission the temperature was 99.6° C., the blood pressure by the flush method 52 mm. Hg in the right arm, 54 mm., in the left arm, 62 mm. in the right leg, and 66 mm. in the left leg. The pulse rate was 160 and the respirations 54 per minute. The infant was well developed, well nourished, and in no distress, but cyanotic when not given oxygen. The chest was clear to percussion and auscultation. The examination of the heart showed a right ventricular type of impulse. The first sound was not remarkable; the second sound was heard best at the left sternal border where there was also a grade I systolic murmur. The liver was palpable 4.0 cm. below the right costal margin. It was not pulsatile. The spleen tip was palpable. There was early clubbing of the fingers and toes. The remainder of the physical examination was noncontributory.

On laboratory examination the urine was normal. The hemoglobin was 18 Gm. per cent, the peripheral leukocyte count was 23,650 per cubic millimeter, with a differential smear of 48 per cent polymorphonuclear cells, 8 per cent basophils, 28 per cent lymphocytes, 12 per cent monocytes, and 4 per cent eosinophils. The platelets were normal in number. The serum nonprotein nitrogen was 39 mg. per cent. The Hinton reaction was negative. Fluoroscopy of the heart revealed a globular shadow, at the upper

limit of normal in size, with an elevation at the apex. There was a marked depression in the region of the pulmonary artery and no main pulmonary artery could be identified. The intrapulmonary vasculature was decreased in prominence. The right atrium was increased in size. The aorta was prominent and normal in position. An electrocardiogram showed right ventricular hypertrophy, abnormal for the age. The ST segment and T waves were also abnormal.

The infant, while in the hospital, was gradually weaned from oxygen therapy. He was given digoxin and Gantrisin. He did well and was discharged from the hospital after a nine-day stay.

He was seen frequently in the Cardiac Clinic and continued to do well. The systolic murmur increased in intensity and a continuous murmur was heard by some observers. The cyanosis continued and the size of the liver remained unchanged. The electrocardiograph displayed changes of a progressive increase in the right ventricular pattern and a P pulmonale. Right bundle branch block and digitalis effects were present in all tracings. The cardiac fluoroscopy findings remained unchanged. At 10 months of age, nineteen days before death, the infant was seen in the clinic. He weighed 16 pounds and, though no murmurs were heard, the general condition was unchanged.

Eight days prior to death, the child had two mild and one severe cyanotic spells, which responded to morphine. On the day of death, another cyanotic spell occurred while attending the clinic. Then no murmur was heard and the liver was 5.5 cm. below the costal margin. Morphine and oxygen were given, without benefit, and the infant died, on admission to the hospital, at 11 months of age.

DISCUSSION

DR. PATRICK A. ONGLEY.*—May I first make a few random interpretations of the data as given?

There was said to be a right ventricular type impulse. What is meant by that is that somebody felt the maximal impulse at the xiphoid. That does not mean that this is entirely right ventricular. If there are two ventricles and one feels the maximum impulse at the xiphoid, it is probably right ventricular, but if there is only one ventricle—as in a tricuspid atresia, or single ventricle from any other cause—then you may feel the maximum impulse at the apex or at the xiphoid, so I think it would be correct if one said that this was a xiphoid-impulse. The first heart sound was described as being not remarkable, and the second sound was loud at the lower left sternal border. We are more interested in knowing what the second sound was like at the pulmonary area, and if it was a split sound or a single second sound.

DR. PETER AULD.—The pulmonary second sound was single.

DR. ONGLEY.—Was it diminished at the pulmonary area? If the second sound is split, that usually implies that there are at least two functioning valves. If there is a single second sound, one valve may be functioning well (which you can hear) and there may be one which you cannot hear. The murmur described was a grade I

*Dr. Patrick A. Ongley was formerly instructor in Pediatrics, Harvard Medical School, and Assistant Cardiologist, The Children's Medical Center.

soft systolic murmur over the lower left sternal border. That does not help us at all because any normal person can have a grade I systolic murmur at the lower left sternal border. A suggestion of early clubbing of the fingers and toes was reported. We usually do not see true clubbing until at least a few months after birth, usually five or six, so I think the suggestion of early clubbing in a patient who is only mildly cyanotic does not help us at all. I would like to know the degree of cyanosis. It seems that it was not particularly marked at any time. Would that be a fair statement, Dr. Auld?

DR. AULD.—That is correct.

DR. ONGLEY.—I have just now looked at the electrocardiogram. The term P pulmonale usually refers to rather tall P waves, more than 2.5 mm. in height in Leads II, III, and those from the right chest. It is usually thought to mean right auricular hypertrophy. However, the P waves are not particularly tall in Leads I and II and, in fact, are just as big in Leads V_2, V_3, V_4, and V_5. I think that all we can infer from this is that we have atrial hypertrophy, but we do not know whether it is right or left, after looking at the tracing. The electrocardiogram, while it shows right ventricular hypertrophy, does not show the nice tall, narrow, right ventricular potentials which you see in pure pulmonic stenosis. It shows a rather wide QRS complex, which is the type that we sometimes see in a single ventricle.

Now let us consider the x-rays. There are certain things that I would like to ask Dr. Wittenborg. First: Are you sure this is the right atrium? Second: In your reports you say that the position of the aorta is normal, and I would like to know if, in the lateral film, it could be anterior to the normal position? In other words, could it be transposed? Third: Did you see a right and left pulmonary artery, or do you think there is a collateral pulmonary arterial pattern?

DR. MARTIN H. WITTENBORG.—The best films, Dr. Ongley, were taken at 6 days of life. We have a definite globular configuration in a heart which is only slightly enlarged in transverse diameter. The waist normally occupied by pulmonary artery is exceedingly narrow. This would imply that the pulmonary artery is markedly hypoplastic, completely absent, or that it is malposed. On the oblique films there was no unusual widening noted at the waist, so that it is assumed that the pulmonary artery is hypoplastic or absent. The aortic arch is on the left and the aorta descends in the normal manner. At this age it is impossible to determine accurately, by fluoroscopy, slight anterior take-off or slight dextropositions of the aorta. The pulmonary vasculature is definitely diminished, the vessels being small in caliber.

Later films show very little increase in the size of this heart, the shape remains the same, the vasculature remains diminished, and the right auricle is not demonstrated. The fluoroscope indication is that the heart was unduly prominent on the posterior lateral aspect, toward the posterior axillary line; when you rotate the patient, the right auricle would lie posteriorly.

DR. CRAIG.—Did you see the left atrium?

DR. WITTENBORG.—No mention of enlargement of the left atrium is made,

but the heart must have been unusually prominent posteriorly on the right. For this reason we mentioned a selective right auricular enlargement. We tend, in this hospital, to pay little attention to auricular enlargement because we find that it is of little value in the differential diagnosis. Especially, we do not try to distinguish the right from the left atrium. I think the films should probably be interpreted as showing prominence in the region occupied by atria.

DR. ONGLEY.—At the time this child entered the hospital, the first diagnosis one would consider would be a tetralogy of Fallot, that being a common cause of cyanosis with evidence of right ventricular hypertrophy, a protruding apex, and a diminished pulmonary vasculature. What is against this diagnosis? There are two things, primarily. The first is that he does not have a murmur which really sounds like a pulmonary stenotic murmur. There is only a soft grade I murmur along the lower left sternal border, yet that does not entirely rule out a tetralogy. If such children are examined during a cyanotic spell, or when breathing is particularly heavy, it is difficult to hear the murmur. Assuming that the persistently enlarged liver has been due to congestive failure, then we must assume that we have a tetralogy in failure. We have not seen congestive heart failure in tetralogy of Fallot in childhood, so I think we will discard that diagnosis.

The second lesion that one thinks about is valvular pulmonic stenosis with an intact ventricular septum, and a right-to-left shunt through a patent foramen ovale. The finding against this is that no pulmonary artery is seen. Now it is true that we have seen cases of pure pulmonic stenosis which did not show any obvious pulmonary artery by roentgen examination. One 6-month-old girl had a markedly enlarged heart, and as the heart enlarged it obscured the origin of the pulmonary artery—but we do not have that type of x-ray picture here.

The third diagnosis would be tricuspid atresia. In our series of tricuspid atresias we have two which showed right ventricular hypertrophy on the electrocardiogram. If you are going to diagnose tricuspid atresia in the presence of right ventricular hypertrophy, you will be wrong so often that is not going to make very much sense. I would prefer to disregard tricuspid atresia as a possible diagnosis, even though there is a very remote chance that this may be the proper diagnosis.

A fourth possibility is a true truncus arteriosus. There is not too much that is against a true truncus—one large single vessel is identified coming out of the heart—yet the patient was not very cyanotic in the early stages of life. When we see a true truncus patient who is not very cyanotic, we usually find very good pulmonary vasculature and a continuous precordial murmur. If the pulmonary arteries are very small, a continuous murmur may not be present. Even so, these patients are often considerably more blue than this child was. A truncus, I think, is a very distinct possibility.

Last, I really want to consider something else which is a little bizarre, perhaps. It puts me way out on a limb but would possibly explain everything that we find, including a cause of

death. If we assume that there is no visible pulmonary artery segment on x-ray, then, as Dr. Wittenborg says, we either have no pulmonary artery at all, or we have a small hypoplastic one, or we have one which is completely displaced. Now, if we have a displaced one—in other words, a typical transposition—we then usually have pulmonary vascular engorgement, which we do not have here. If, on the other hand, we have a displaced pulmonary artery but with pulmonary stenosis, we should hear a pulmonary stenotic murmur—but we do not hear that either. We have to take things on their face value and are going to assume that we have pulmonary atresia. By pulmonary atresia we mean atresia of the pulmonary valve; we do not mean that the pulmonary arteries themselves, beyond that valve, are necessarily going to be absent. The developmental anomaly which causes the atresia of the valve is not necessarily going to cause disappearance of the entire pulmonary arterial system. If we have pulmonary atresia, then we are going to have to get some blood back to the lungs, somehow, and we have two choices, either through bronchial collateral arteries or through a patent ductus. Now, if bronchial collaterals are present, one may hear a continuous murmur out in the periphery of the lung fields, either in the axillae or over the back, but the only continuous murmur we have recorded here is one heard along the left sternal border, and we do not see any bronchial collateral pattern on the x-ray. Therefore, I am going to assume that we have a single ventricle, an aorta leading out from this, and then a ductus going down from this aorta to the pulmonary arteries. We now have the blood to the lungs, and we have to get it back to the left atrium. I am going to assume that the pulmonary venous drainage is normal, although in some cases of single ventricle with pulmonary atresia there is anomalous pulmonary venous drainage. Up to this stage I am reasonably confident of the diagnosis of a functionally single ventricle with one vessel—the aorta leaving this ventricle and the blood passing via a patent ductus arteriosus to the pulmonary arteries. From here, we must go on statistics.

If there is a single ventricle, then there is a great likelihood of a single ventricle with pulmonary atresia or, in some cases, aortic atresia. Here we think it is going to be pulmonary atresia because of the diminished vasculature. Isolated single ventricles with normal atrioventricular valves are rare. Mitral atresia or tricuspid stenosis is commonly present. Since there is no diastolic murmur suggesting tricuspid stenosis, we are going to assume that this patient has mitral atresia as well.

This brings us to a consideration of the atrial shadow in the x-ray. I would like this to be a large left atrium since, when mitral atresia is present more commonly, there is a patent foramen ovale rather than a secundum-type atrial septal defect. If the foramen ovale becomes stretched a little, a left-to-right shunt through this stretched orifice, rather than through a true secundum-type atrial defect, may be present.

These, then, will be our anatomical diagnoses—single ventricle, pulmonary atresia, a transposition of the great

vessels, a patent ductus arteriosus, and a mitral atresia, probably with a patent foramen ovale.

Can we say now why the patient died? We have a reasonably good flow to the lungs. Anatomically we have a normal venous return, and we have a functionally trilocular heart—so the patient should not do too badly. Now, if this patient were a little older, I would think, first of all, of a cerebral abscess as the cause of death. There have been quite a few cases in the literature of this type of lesion with a cerebral abscess, but this child was only 10 months of age. On the other hand, if we try to assign death to a physiologic disturbance, a patent foramen ovale will give an increased pressure in the left atrium, and this is transmitted to give an increased capillary pressure and pulmonary arterial pressure. This could cause death in two ways. It could cut down the left-to-right shunt through the ductus and cause these anoxic attacks of blueness and death in that way—or a thrombosis could occur in the pulmonary artery, resulting in death.

DR. CRAIG.—Do you ever get pulmonary congestion with mitral atresia?

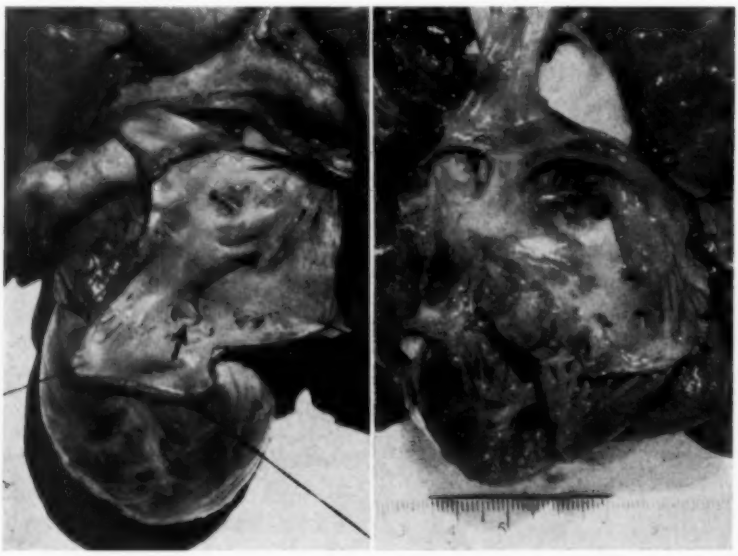

Fig. 1. Fig. 2.

Fig. 1.—Heart. The left atrium is viewed from above. The endocardium is thickened. At the arrow is the mitral valve remnant leading to the hypoplastic isolated left ventricle.
Fig. 2.—Heart. The right atrium and ventricle are dilated, the ventricle is hypertrophied.

DR. ONGLEY.—Well, I do not see why you couldn't get it secondary to difficulties with outflow from the left atrial chamber. Is there any venous congestion of the lungs?

DR. WITTENBORG.—I think that on the second film the vasculature is slightly more prominent, with pulmonary engorgement.

DR. LOUIS K. DIAMOND.—Dr. Ongley, what therapy would you recommend for this child?

DR. ONGLEY.—I am surprised that he lived this long. The average duration of life is about three or four months.

DR. CRAIG.—This child, at autopsy, had functional mitral atresia with a very small mitral valve remnant opening into a minute isolated left ventricle, with no other openings (Figs. 1 and 2). The pulmonary veins were dilated, as was the left atrium; the endocardium of the latter was thickened. The aorta was transposed and the pulmonary outflow tract was atretic, both as Dr. Ongley predicted (Fig. 3). The pulmonary artery was of good size and the ductus arteriosus was patent, having a diameter of 3 mm. There was a pulmonary artery thrombus and resulting lung infarction. The latter may have been partially due to the increase in pulmonary venous pressure as a result of the absence of an adequate outflow from the left atrium.

The child had evidence of cardiac failure with passive congestion of the liver. Numerous stercoral ulcers were present in the bowel, which may be correlated with the child's history of constipation which was not brought out, I believe, in the clinical procotol. These ulcers may not have been of clinical importance.

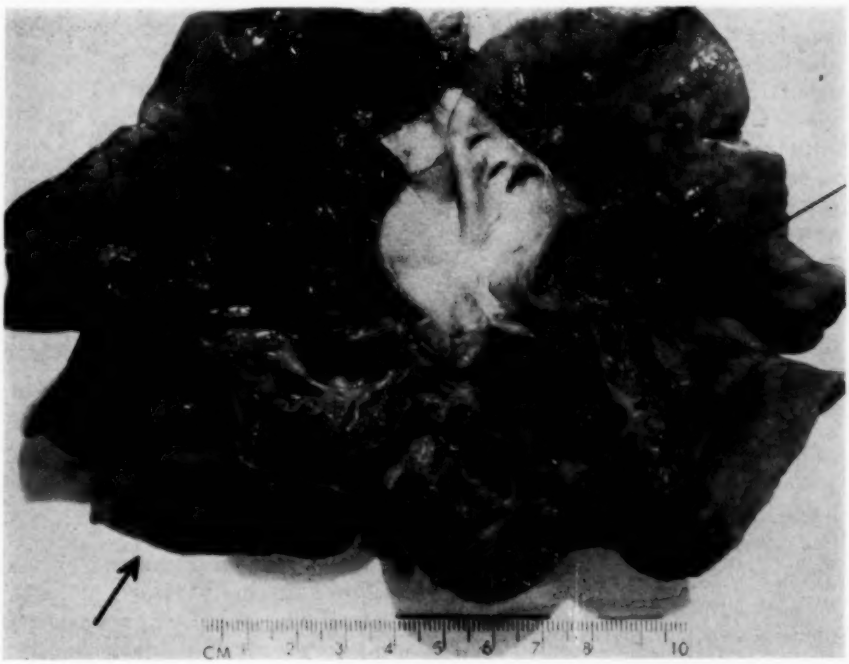

Fig. 3.—Heart and lung. The transposed aorta comes off the right ventricle anteriorly. The right lower lobe of the lung is infarcted.

The lesions of mitral atresia are, in many ways, complementary to those of absence of the tricuspid valve in that one may have transposition or hypoplasia of the outflow tracts of either ventricle. An incomplete summary of our autopsied cases of mitral atresia (in which there were eight examples) indicates that aortic hypoplasia was present in three, pulmonary hypoplasia or atresia in four, and, in one instance, the ventricular outflow tracts were of equal size. In five cases, the left ventricle was isolated, without connections to other heart chambers; in the remainder, the left ventricle was hypoplastic. Three had no atrial septal defect, though in one of these there was anomalous venous damage to the right atrium. In the reported cases with no free interatrial communication, the return of blood from the lung may pass through enlarged Thebesian channels, extra-atrial channels, or by the bronchial veins to the right ventricle. The duration of life in our cases of mitral atresia is, on the average, three to four months, as mentioned by Dr. Ongley. At autopsy we have seen one girl of 17 years, however, who had mitral atresia. In her case, a diagnosis of Fallot's tetralogy had been made. She succumbed with a pulmonary artery thrombosis after a Potts' aortic-pulmonary anastomosis.

In the case under discussion, the pulmonary artery was adequate in size for an anastomosis.

DR. ABRAHAM RUDOLPH.—In cases with a decreased pulmonary flow but with a large heart, there is almost always a complicated heart lesion. If an aortic-pulmonary shunt is performed to help these children, they usually succumb to the procedure fairly soon. With a shunt, a great deal of the blood which is going out through the aorta will come back to the ventricle, and the ventricle will have a tremendously increased amount of work to do. The ventricle often goes into failure within six months after operation. We have seen this with a single ventricle and a decreased pulmonary flow. If one had put a shunt into this baby, there would have been the extra problem of getting the blood back from the lungs to the right atrium.

One other interesting point is that in spite of the large pulmonary veins that were seen at autopsy, on the x-ray we could not really see any pulmonary veins, which again bears out the point that it is not the size in terms of anatomical size, but the size in terms of flow. This is of some importance because the flow through this must have been very small. I think Dr. Ongley did a wonderful piece of detection.

DR. CRAIG.—After a shunt procedure in tetralogy of Fallot, is the work load of the right ventricle reduced?

DR. RUDOLPH.—Well, actually this is something which people are thinking a great deal about in relation to the degree of overriding of the aorta. At one time it was thought that the degree of overriding was a significant feature. Then, suddenly, thinking changed and the relative resistance of the systemic circuit and the pulmonary obstructions were regarded as most significant as to the degree and direction of the interventricular shunt. However, when you consider the fact that if the aorta is overriding considerably, even if there is a fairly large ventricular defect, the actual streaming of blood must push blood from the

right ventricle into the aorta. In the tetralogy patients, as a group, the ones who go into failure after shunt surgery (though perhaps Dr. Gross will not agree with me) are those who have marked overriding of the aorta and a large ventricular defect. On the other hand, with a very small ventricular septal defect, you may not actually do a great deal of good by a shunt procedure. If the aorta has little overriding, and the ventricular septal defect is small, putting in a shunt will not really help very much because the degree of shunt from right to left is quite small.

Dr. Robert E. Gross.—With some cases of the mitral atresias, with a large pulmonary artery, too much blood gets into the lung. These children will, eventually, if they live long enough, get right-sided heart failure.

Dr. Craig.—The usual embryological explanation for mitral atresia is the one which is given for tricuspid atresia—that there has been a deviation in the formation of the septum of the atria and ventricle, primarily of the ventricle, to one side, so that the atrioventricular canal is obliterated on the side of the atresia.

Medical Progress

HEMISPHERECTOMY IN CHILDREN

ARTHUR M. KAPLAN, PH.D.
ST. LOUIS, MO.

INTRODUCTION

BOTH the pediatric practitioner and the neurosurgeon are frequently confronted by parents who raise very practical, important, and difficult questions. To the parent who must make a decision regarding such drastic surgery as a hemispherectomy, consequences are of primary importance. As unhappy as parents are with a child's hemiplegia, endless convulsions, and incorrigible behavior, the thought of surgery evokes certain anxieties and fears which must be dealt with by the pediatrician and/or neurosurgeon. The probability of surgical survival is always uppermost in the minds of parents whose children undergo such major surgery. The next question is usually, "What effect will such surgery have on my child's behavior?" The question of surgical survival can be answered objectively in terms of probability based upon statistical data. The question regarding consequences of surgery has until recently been answered within the subjective, personal, and anecdotal realm. A definitive study dealing with the consequences of hemispherectomy in children is yet to be done. A start has been made in that a number of studies have begun to utilize objective and standardized measures wherever possible. It is felt that while additional data need to be amassed and sufficient experimental controls utilized, there is sufficient data available at this time to enable the pediatrician to answer some of the questions posed by parents.

From the Division of Medical Psychology, Department of Psychiatry and Neurology, Washington University School of Medicine.

THE APPLICATION OF HEMISPHERECTOMY TO INFANTILE HEMIPLEGIA

Hemispherectomy is a relatively new procedure. The first cerebral hemispherectomy was done by Dandy, in 1923, at the Johns Hopkins Hospital, and this case first appeared in the literature in 1928[1]—just 30 years ago. Since that time, numerous case reports have appeared. Mensh and his associates[2] listed 32 publications between 1928 and 1951. These represented 41 hemispherectomies. While a preponderance of this surgery was applied to the adult suffering from infiltrating tumors of the subdominant hemisphere,[1-12] hemispherectomy has of late been utilized and applied to a specific group—the infantile hemiplegic.[13-26]

Ford[27] classifies this condition as one of either acute infantile hemiplegia of obscure etiology or congenital hemiplegia. Regarding the acute type, Ford states:

> In the early stages of the illness the affected hemisphere may be so swollen that ventriculographic study may suggest brain tumor. Later, of course, atrophy becomes evident. Later the hemiplegia extremities become spastic and the usual deformities develop. The affected limbs do not develop as well as the normal limbs and years later may be very small and distorted. Tremor or athetosis may appear. In other cases, the focal signs may largely or completely disappear. Unfortunately, in almost half of all cases convulsive seizures recur from time to time.

The prognosis as presented by Ford is one of low mortality and is unfavorable in outlook for recovery. Epilepsy is said to follow in about half of all cases, and mental retardation is to be expected. This type of hemiplegia is said to result from a single gross vascular lesion of the brain.

The congenital form of hemiplegia is said to result from a birth injury. Intrauterine injury and disease are other explanations offered. Ford describes the clinical features of the congenital type as follows:

> Flaccidity of the paralyzed limbs is relatively more frequent in congenital hemiplegias than among those occurring later in life. In such cases, we find striking under development of the hand and less evident under development of the arm and leg. The hand is of childish appearance, but it is not in any way deformed. Due to the shortening of the leg the pelvis may be tilted and the spine may show a postural curve. The tendon reflexes are usually somewhat increased on the affected side, but this is never so striking as in spastic paralysis.
>
> In other cases, the paralytic limbs are very spastic since the muscle spasm develops when the bones are plastic, extreme deformity of the hand is produced.
>
> In almost all cases, there is mental deficiency—convulsive seizures occur in almost 40 or 50 per cent of all cases.
>
> Even severe hemiplegias of congenital origin may not be apparent until the child is several months of age.

The prognosis is said to depend upon the amount of injury to the nervous system. "Little improvement is to be expected. The presence of convulsions makes the outlook unfavorable, for deterioration often occurs in such cases."

It would certainly seem from the above that the prognosis of infantile hemiplegia accompanied by convulsive seizures is indeed gloomy. It is with this in mind that surgical intervention occurred. Krynauw[19] worked primarily with children and carried out twelve hemispherectomies over a five-year period. In all cases, hemiplegia per se was not a sufficient condition for surgery. Convulsive seizures and behavioral changes (uncontrolled emotional outbursts) were also evident. Thus, a triad of symptoms were considered before hemispherectomy was undertaken—hemiplegia, convulsive seizures, and the presence of lowered intellectual functioning and/or uncontrolled emotional outbursts as behavioral manifestations. Occasionally, surgery was undertaken in the absence of seizures or in the absence of emotional outbursts while the other symptoms were present. Thus, it was only a little over seven years ago that any specific formulation developed in the application of hemispherectomy to children.

FINDINGS

A survey of the American and British literature pertaining to hemispherectomies in children (ages from birth to 16 years) yielded 29 cases. Table I summarizes the data reported by each investigator. It is interesting to note that investigators differ in the amount and kind of information reported. For example, one investigator[19] relied on parental report and subjective evaluation of change in intellectual functioning. Another investigator[25] focused on the social adjustment of the child and reported no data regarding the particular hemisphere removed, the effect on the child's seizures, and hemiplegia. Still another investigator[23] concluded that intellectual functioning increases following hemispherectomy, yet gave no specific data to support his conclusions. While systematic and quantitative measures are at times lacking and like the blind men, each investigator touches a different part of the huge elephant, the impressions and findings that are reported do seem to indicate specific trends. Tables II-VIII present these trends.

TABLE I. EFFECTS OF CEREBRAL HEMISPHERECTOMIES IN CHILDREN

AUTHOR	AGE AT HEMISPHERECTOMY	SEX	HEMISPHERE REMOVED	CONVULSIVE SEIZURES	HEMIPLEGIA	INTELLECTUAL FUNCTIONING	EMOTIONAL OUTBURSTS
Krynauw (1950)	9	F	L	Gone	Improved	Improved	Gone
	?	F	L	Gone	No change	Improved	Improved
	3	F	L	Gone	Improved	Improved	Improved
	10	M	L	Gone	Improved	Improved	Improved
	2	M	R		Died		
	9	M	L	None before surgery	No change	Not reported	Gone
	2	F	L	Not reported	Improved	Improved	Improved
	15	F	L	Gone	No change	Improved	None before surgery
	14	M	R		Not reported		
	13	F	L		Not reported		
	7 mo.	F	L	Not reported	Improved	Not reported	Not reported
Cairns (1951)	7	F	?	Improved	Improved	Improved	Improved
McKissock (1953)	4	M	R	Gone	No change	Not reported	Gone
	11	M	L	Improved	Worse	Not reported	Gone
	4	M	R	Gone	Improved	Not reported	Gone
	4	M	L	Gone	No change	Not reported	Gone
	1½	M	R	Gone	No change	Not reported	Gone
	13	M	R	Gone	No change	Not reported	Gone
	12	M	L	Improved	Worse	Not reported	No change
	4	F	L	Gone	No change	Not reported	Gone
	8	M	L	Gone	No change	Not reported	Gone
	9	F	R	Gone	No change	Not reported	Gone
Fleischacker (1954)	12	M	L	Improved	Worse	Not reported	Improved
	13	M	R	Gone	Improved	Not reported	Improved
	12	M	L	Improved	No change	Not reported	No change
Uecker (1954)	13	F	?	Not reported	Not reported	No change	Improved
	13	M	?	Improved	Not reported	No change	Improved
	15	M	?	Gone	Not reported	No change	Not reported
Munz & Tolor (1955)	14	F	L	Gone	No change	No change	Gone

Of the 29 hemispherectomized children, one or 3 per cent died. This occurred to a 2-year-old male and is reported by Krynauw.[19] His condition is said to have given no cause for alarm during surgery. He became very restless while returning to the ward and suddenly collapsed and died. Thus, the mortality rate as a function of surgery is seemingly low.

TABLE II. AGE DISTRIBUTION OF ALL CASES REPORTED IN THE LITERATURE

AGE DISTRIBUTION	N	%
<1 year	1	4
2 years	2	7
3 years	1	4
4 years	4	14
5 years	0	0
6 years	0	0
7 years	1	4
8 years	1	4
9 years	3	10
10 years	1	4
11 years	1	4
12 years	3	10
13 years	5	17
14 years	2	7
15 years	2	7
16 years	0	0
No age reported	1	4

Table II indicates that the cases reported in the literature are drawn from all age groups except years 5 and 6. When the sample is categorized into preschool (ages from birth to 6 years), middle childhood (ages 7 to 12 years) and adolescence (ages 13 to 16 years) we find little difference between the number included in each developmental category. For 27 reported ages, 30 per cent come from the preschool group, 37 per cent from the middle childhood group, and 33 per cent from the early to middle adolescent period.

According to Tables III and IV, boys underwent hemispherectomy more often than girls, and the left hemisphere was reportedly removed more frequently than the right one. The sex differences may not necessarily be significant since these differences are relatively small. There does, however, appear to be a greater proclivity for the left hemisphere to be removed. More than half of the cases consisted of the removal of the left hemisphere. Of the 26 cases in which the particular hemisphere removed is indicated, 19 or 65 per cent referred to the removal of the left hemisphere. Ten per cent failed to indicate which hemisphere was removed.

TABLE III. SEX DISTRIBUTION OF ALL CASES REPORTED IN THE LITERATURE

	N	%
Boys	17	59
Girls	12	41

TABLE IV. HEMISPHERE REMOVED

HEMISPHERE REMOVED	N	%	(% OF REPORTED CASES) N = 26
Left	17	58	65
Right	9	32	35
Not reported	3	10	

TABLE V. THE STATUS OF CONVULSIVE SEIZURES FOLLOWING SURGERY

STATUS OF CONVULSIVE SEIZURES	N	%	(% OF REPORTED CASES) N = 20
Completely gone	15	52.0	75
Improved	5	17.0	25
No change	0	0.0	
Absent before surgery	1	3.5	
No data reported	7	24.0	
Expired	1	3.5	

Table V indicates that a major consequence of hemispherectomy is the absence or reduction of convulsions. While close to one fourth of the reported cases did not deal with the pre- and poststatus of convulsions, of the

20 cases which did deal with this variable, 75 per cent no longer experience convulsions, and 25 per cent are improved in that the frequency and/or intensity of the convulsions have diminished. This is one very positive finding. Of the three presenting complaints usually considered as the criteria for hemispherectomy, one may very well be able to predict that convulsions will become extinct or at least become greatly reduced in severity in all or at least in the majority of cases.

A second criteria for hemispherectomy, hemiplegia, is more difficult to assess. Investigators focus on different aspects and with more or less specificity. When the findings are categorized in a general way according to improved, no change in status, or condition worse following hemispherectomy, the results are less fortunate than is the case with convulsions. Table VI indicates that of the 23

TABLE VI. THE STATUS OF THE HEMIPLEGIA FOLLOWING SURGERY

STATUS OF HEMIPLEGIA	N	%	(% OF REPORTED CASES) N = 23
Improved	8	28	35
No change	12	41	52
Condition worse	3	10	13
No data reported	5	17	
Expired	1	4	
	29		

cases in which this variable is considered, 35 per cent showed some form of improvement. This varied behaviorally from improved balance to decreased spasticity of the affected limbs. Fifty-two per cent did not show any change, and 13 per cent became worse. The hemiplegia became worse in two cases reported by Mc-Kissock.[23] He states, "[Cases Nos. 2 and 7] suffered as a result of operation: both of these were errors of judgment on my part. One developed an increase in hemiplegia which has fortunately been offset by disappearance of the severe behavior disorder, whilst the other has acquired an increased speech defect. This latter case should have been subjected only to a local excision of abnormal parietal cortex rather than to ablation of the hemisphere." Thus, while occasionally one can expect worsening of the hemiplegia, in 87 per cent of the cases the patients were no worse off and some (35 per cent) improved.

The third criteria, emotional outbursts, also diminish to a great extent. Table VII indicates that of 24 cases in

TABLE VII. CONTROL OF EMOTIONAL OUTBURSTS

STATUS	N	%	(% OF REPORTED CASES) N = 24
Improved	21	72	87
No change	3	10	13
Worse	0	0	
None present prior to surgery	1	4	
No data reported	3	10	
Expired	1	4	

which severe emotional outbursts are reported prior to surgery, 21 or 87 per cent show improvement in this area. Only 13 per cent of the reported cases indicate no change in behavior. In no case did this behavior become worse. It would seem then that along with control of convulsions, one can anticipate effective control of emotional outbursts.

Little systematic attention has been given to the actual measurement of

intellectual functions. While the consensus of opinion seems to be that intellectual functioning improves as a result of hemispherectomy, few studies[13, 22, 25] have actually reported objective measurements. Table VIII indicates that no data were reported with respect to intellectual functioning for 58 per cent of the cases. While close to one fourth report improvement, 86 per cent of these are based upon subjective evaluations. Of the 14 per cent who report no change in intellectual functioning, only 50 per cent are based upon subjective evaluations—the other 50 per cent being based upon objective measurements. Assessing this variable is extremely complex. No one can measure intelligence per se but only the functions of intelligence as manifested in behavior. What is being measured is intellectual functioning and not native intelligence. The latter is inferred; the former is observed and ascertained through standardized and objective measures. The appraisal of intellectual functioning is further complicated by the numerous factors which alter one's level of functioning. Some of the more important factors are: the ability to see and hear; level of motivation including the desire to cooperate and do as well as one is able; and adequate control of impulses. Howells and Kay[28] state:

TABLE VIII. THE STATUS OF INTELLECTUAL FUNCTIONING FOLLOWING SURGERY

STATUS OF INTELLECTUAL FUNCTIONING	N	%	NUMBER BASED UPON IMPRESSION	NUMBER BASED UPON OBJECTIVE MEASUREMENTS
Improved	7	24	6	1
No change	4	14	2	2
Worse	0	0	0	0
No data reported	17	58		
Expired	1	4		

> In our experience in testing cases of infantile hemiplegia before operation we have become aware of the difficulties involved in ascertaining reliable and stable indices of the intellectual ability. In particular, we have noted that as well as the child's physical handicap in completing performance tests, his frequent distractibility, memory defects, short lapses of attention, lack of confidence, and perhaps also his often considerable gap in formal education, have lowered his test results to an undetermined extent.

In view of these many variables, one needs to be cautioned against conclusions which infer that native intelligence rather than intellectual functioning becomes or does not become elevated. Krynauw[19] indicates:

> Improvement in the mental sphere presupposes and is dependent upon, the integrity of the remaining hemisphere and its ability to function normally once it has been released from abnormal influences from the pathological side.

It would seem then that once the pathology is removed and the motor "driveness" of the individual restored to a more stable level, intellectual functioning as measured by standardized tests, is able to become more adequately maximized.

DISCUSSION

A review such as this brings to the fore many questions and problems for the researcher in this area. While investigators are idiosyncratic in their interests and necessarily focus on different aspects of the problem, there is a need for greater systematization in reporting clinical case accounts if a complete understanding of the hemispherectomized patient is to be

achieved. This discussion will consider the ways in which investigators can communicate and make their findings more meaningful to others as well as present suggestions for future research. It would seem that all investigators should report their face sheet data, i.e., a patient's age, color, religion, socioeconomic level, etc. Furthermore, one would need to consider dominance, presenting symptoms, the specific time in the total course of study when certain observations are made, and the particular hemisphere removed. These data are available to all and should be reported if systematic comparisons are to be made between investigators. If a follow-up study is done one would also need to indicate the sources from which particular data stem and the time factor in relation to the date of hemispherectomy. Thus, it is important to indicate whether the investigator is reporting his own observations based on specific tests or is reporting anecdotal material related by the patient's family. One would also need to indicate whether the observations are made while the patient still resides in the hospital or as an outpatient. There is also a tendency to speak collectively of drugs rather than to specify particular drugs and dosage. It is insufficient to indicate that a patient no longer has seizures following hemispherectomy. One also needs to spell out to what extent this is evident when the patient is maintained on anticonvulsive drugs and to what extent this is so when the patient is free of drugs. There are also investigators who describe in a general manner that a child has emotional outbursts, but there are no indications as to what situations instigate the outbursts and just what the outbursts entail. Also, quantitative measurements should be utilized whenever possible. It was pointed out earlier that subjective evaluations are made regarding intellectual functioning and also regarding the appraisal of social and emotional development and adjustment. This is unfortunate since there are tools available[29, 30] which can quantitatively measure changes in specific intellectual functions such as general fund of information, comprehension, arithmetical reasoning, immediate recall, vocabulary, planning ability, perceptual skills, visual-motor coordination and integration, and ability to handle abstract ideas. In like manner, there are scales which can measure social development,[31] and projective techniques[32, 33, 34] which can measure specific personality variables such as hostility and aggressivity, ability to relate to others, needs and need systems, self-concept, etc. Thus, if one is to follow a pre- and postoperative research design, one must be very specific regarding the sample used, the time of observation, as well as the sources and tools of observation. Measurement per se is not invariably more useful than description. Descriptions have a very definite place; however, if descriptions are to be useful, they must elucidate very clearly and specifically that which is being observed. It is only in this way that one investigator can directly compare his findings with that of another investigator. A great deal of emphasis has been placed in this discussion on the importance of indicating the time when particular observations are made. Research upon the hemispherectomized

patient necessarily entails a longitudinal kind of research design. Unless the time factor is clearly specified, cross validation becomes especially difficult.

One can certainly question the validity of the findings reported in this paper since the emphasis and interests of the investigators proved to be so varied. While this is true, there were nevertheless consistent findings even for so varied a group. Thus, epileptic seizures were greatly reduced in all of the studies regardless of the investigator. This was also true regarding emotional outbursts. While the findings reported here may be considered general, they nevertheless emphasize the need for more specific and systematized research.

There are several ideas which come to mind at this time regarding suggestions for future research. Since hemispherectomy has been extended to all age levels it would be interesting to investigate to what extent the prognosis differs from one age level to another when the presenting complaints are similar—hemiplegia, intractable seizures, emotional outbursts, and mental retardation. When the present data were analyzed for three age levels (preschool, middle childhood, and adolescence), it was found that there were no differences in the consequences of hemispherectomy in so far as status of seizures, status of hemiplegia, and status of emotional outbursts are concerned. These must be considered fairly tentative findings since tests of statistical significance could not be applied due to the many zero cells and the relatively small number of cases. In like manner, consequences of surgery can be systematically evaluated for sex differences, dominance, and the particular hemisphere removed. It was reported that there was a greater tendency for the left hemisphere to be removed than the right. This finding in and of itself is meaningless but does raise questions which can be pursued if enough systematic data are available. To those who feel that hemispherectomy greatly improved intellectual functioning, one could certainly study and evaluate the cases where this occurs and those where this does not occur. With the aid of objective measurements, one could even determine how much or how little change occurs. A study also needs to be done with regard to those cases whose hemiplegia improves and those who do not improve.

Medicine has become a comprehensive field in that it is becoming more and more concerned with the treatment of the total person. Thus, the pediatrician is concerned with the illness of the patient but is also becoming concerned with the patient's reaction and adjustment to his illness. We are beginning to see more and more the need for guidance in the treatment of patients who have undergone hemispherectomy. Their entire way of life needs to be restructured, relearned, and new goals established. This can be done only with the aid of the physician who is treating the patient. In the case of the child who is undergoing hemispherectomy, both the pediatrician and the neurosurgeon need to understand the total consequences of surgery—social, economic, and medical if he is to help bring about an effective adjustment for the child and his family. Research in this area will

need to be interdisciplinary and findings pooled, since pediatrician, neurosurgeon, neurologist, psychologist, and psychiatrist each contribute to the total understanding of the patient. So long as each specialty works independently, a total Gestalt will be lacking. Systematized and well-controlled interdisciplinary research will no doubt prove to be more fruitful in the end.

CONCLUSIONS

What information then can the pediatrician and neurosurgeon impart to the parents of hemiplegic children who are being considered for hemispherectomy? It would seem that he could point out that research findings dealing with children tend to indicate a low surgical mortality rate, a very good chance that intractible seizures will become extinct or greatly reduced in number and severity, and more adequate control of emotional outbursts. The prognosis of the hemiplegia itself is indeterminant at this time although some do improve. While mental retardation is certainly not cured by hemispherectomy, it seems reasonable to suppose that more optimal intellectual functioning will ensue if the hypertonic behavior of the individual prior to surgery interfered with the efficacy of his intellectual functioning and is absent following surgery.

SUMMARY

This paper reviews the British and American literature regarding the application of hemispherectomy to children suffering from infantile hemiplegia, intractable seizures, emotional outbursts, and mental retardation. While investigators differ in the amount and kind of information they report, certain trends are evident when the 29 cases are evaluated in terms of consequences of surgery. There seems to be a low surgical mortality rate, decrease or extinction of seizures, more effective control of emotional outbursts, and, in some cases, improvement in the hemiplegia itself.

Consideration is given to ways in which research in this area can be made more systematic and more adequately communicated. Suggestions for future research are also presented.

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Comments on Current Literature

HYPOPHOSPHATASIA

The association between deficient bone formation and low alkaline phosphatase activity in the serum and tissues was first recognized as such by Rathbun[1] in 1948. Various clinical aspects of the condition, called hypophosphatasia by Rathbun, had been recorded earlier. Subsequent reports, some of which used the terminology, low phosphatase rickets, indicated that this bone disorder is more common than was suggested originally. At the present time a clearer concept of hypophosphatasia as a disease state is emerging, particularly with reference to its differentiation from vitamin D resistant rickets, and from osteogenesis imperfecta, both of which may be accompanied by changes in the teeth. Rathbun's original case was that of a male infant, seen first at 3 weeks of age, who was admitted to the hospital because of failure to gain weight and apparent pain on handling. In this young infant, defective mineralization of the skeleton was quite evident, with marked rachitic changes in the bones and diminished serum alkaline phosphatase activity. The low level of alkaline phosphatase persisted through six weeks of hospitalization, during which the infant was under vitamin D therapy, supplemented by thyroid and testosterone. At the time of necropsy, diminished alkaline phosphatase activity in the tissues was demonstrated. Pathologic bone lesions were described as indistinguishable from those associated with vitamin D resistant rickets.

Cases reported since 1948 have attested to the wide variability in age of onset in this condition—from birth, to adolescence, to adult life. In one instance reported by McCance and his associates,[2] defective mineralization of the skeleton was suspected before birth by x-ray examination. At birth the infant showed changes in the long bones, a poorly developed bony cranium with widely separated and communicating fontanels, and a flattened chest; beading at the costochondral junctions was noted. An older sibling who died at 14 weeks of age was described as having the same condition. A patient described by Engfeldt and Zetterström,[3] on the other hand, appeared to develop satisfactorily until the age of 3 months, when failure to thrive led to the discovery of a generalized bone disease, which in some respects resembled rickets. Similarly, Sobel and her colleagues[4] reported the case of a well-developed child first seen at 19 months of age. During the two months preceding, several teeth had been shed, and weakness, pain on movement, and deformity of the limbs had become apparent. Onset in still older children has been described.[5, 6] Low levels of alkaline phosphatase activity were noted in two brothers, aged 10 and 13 years, when they were admitted to the hospital for corrective orthopedic procedures.[6] Likewise, cases have been reported in adults of both sexes, in some instances the first sign being premature loss of teeth, or spontaneous fractures, or both.

The *American Journal of Roentgenology* for September, 1957, carried an interesting and well-illustrated article

on hypophosphatasia, the purpose of which was "to outline the major features and to draw a more complete picture of the disease."[7] This report by Currarino, Neuhauser, Reyersbach, and Sobel covers a total of 33 cases of the disease from the literature and from information on some unpublished cases. These authors stress the wide variability with age in both the clinical and the roentgenographic features, and present the findings in three age groups: in newborns, with possible detection in utero, in infants, and in children. Tabulation of the patients according to the age at onset of symptoms revealed that in general the severity of the manifestations decreases as the age of onset increases. Prognosis seems to be poor when the disorder is clearly manifest at birth, or in very early neonatal life. In six newborn infants the clinical features of the disease were essentially the same. "Each was born at term with a globular and 'boneless skull,' soft skeleton, and severe deformities of the extremities."[7] These infants either failed to breathe or had severe respiratory difficulty, and five died within the first hour of life. The sixth lived for nineteen days, showing during this time increasing respiratory distress. Three patients, in whom manifestations were apparent soon after birth, died between the ages of 2 and 6 months. While the skeletal abnormalities in these three were somewhat less severe, they were generalized and were undoubtedly present at birth. Common signs and symptoms included failure to gain weight, slow growth in length and in head circumference, irritability, and jerky movements or convulsions. Prominent features in some instances were cyanosis, fever, sudden episodes of loud crying, anorexia, vomiting, and constipation.

In a group of older infants the symptoms appeared gradually between the first and the sixth months of life, and followed a period of apparently normal development. When the disease appeared in infancy, the outstanding features were failure to thrive, with recurring episodes of unexplained fever, anorexia, vomiting, constipation, irritability, and hypotonia. In some of these infants convulsions and cyanosis were noted. Roentgenologic examination reveals poor calcification of the skeleton; cranial sutures are separated, the anterior fontanel is wide and bulging, and often tense. In some cases there is hypercalcemia with the possibility of renal damage. Prognosis is somewhat more hopeful in the older infant; the bones calcify slowly, symptoms tend to abate, and growth proceeds. However, bony deformity persists in varying degrees and may become more marked with time. Craniostenosis may pose a serious problem, necessitating surgery in some cases. These children walk late and are short in stature; they may experience spontaneous fractures. The teeth are hypoplastic and are shed prematurely. Clinically the survivors from this group merge into the third group of patients composed of older children. This third group included patients who came under observation between the seventeenth month and the thirteenth year of life. In a number of instances, mild manifestations could be traced back to early childhood or to infancy. The usual features included delayed walking, defective gait, painful extremities, dental caries, often rampant, and premature loosening and loss of teeth.

Laboratory findings in hypophosphatasia are not considered abnormal except for the uniformly diminished alkaline phosphatase activity and, in some cases, elevation of serum calcium. One interesting finding, however, is the occurrence in the urine of unusually large amounts of a phosphate ester, phosphoethanolamine.[7, 8] This ester is widely distributed in the cells of many tissues of the body. While the metabolic role of this substance is not clear, the suggestion has been made that its presence in the urine

of patients deficient in tissue alkaline phosphatase activity reflects a disturbance in the functioning of at least one enzyme system.[9]

Therapy in hypophosphatasia has not been satisfactory in general; trials with growth hormone, vitamin C, thiamine, thyroid, and testosterone have not resulted in significant alteration in the clinical evidence of the disease, or in permanent change in phosphatase activity. The use of testosterone is discouraged since in experimental animals a reduction in kidney alkaline phosphatase resulted from its use. While vitamin D in high doses may accelerate mineral deposition, the dangers of hypervitaminosis in the presence of hypercalcemia and kidney damage must be taken into consideration. A recent preliminary report[10] from Canada describing the use of cortisone in a female infant with hypophosphatasia suggests a remission of many of the pathologic features of the disease, but these findings have not been evaluated completely as yet. Studies in rats of the effect of cortisone on serum alkaline phosphatase activity are likewise in the preliminary stage.[11]

On the basis of the more fully investigated patients included in their survey, particularly the roentgenographic and pathologic studies in the different age groups, Neuhauser, Sobel, and their associates[7] conclude that hypophosphatasia is a definite disease entity "quite unlike any other bone disease." Some features resemble those of rickets, of resistant rickets, or of osteogenesis imperfecta, the manifestations varying with age. "Interpretation of the pathogenesis of the disease has been focused principally on the low phosphatase of the serum, bones and other tissues." The discovery of low phosphatase activity in parents or siblings suggests genetotrophic disease, and manifestations at birth or before indicate that the condition may be congenital. Two genetic explanations have been considered possible: the operation of a dominant factor which is intensified in the homozygous state, but expressed in varying degree in the heterozygous individual; or based on a recessive factor which in the heterozygous state is incompletely covered by a normal gene, so that carriers can be detected. In traits having to do with complex enzyme systems, it is more likely that a number of hereditary factors is involved. Physiologic aspects of alkaline phosphatase and its substrates have been studied with reference to bone metabolism.[2, 8, 9] The abnormal metabolite, phosphoethanolamine, has been found in the plasma as well as in the urine of patients with hypophosphatasia. In a very interesting and informative review of the biochemical aspects,[9] one author suggests that a study of such conditions as hypophosphatasia may open the way to a better understanding of many enzyme systems of the body.

RUSSELL J. BLATTNER

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Correspondence

To the Editor:

I have read Dr. Tabrah's gloomy discussion of pediatric practice in the December issue with interest, but with no alarm for the future of pediatrics or pediatricians. I think I can understand what he means, although I do not agree with most of what he says. There is no trade, profession, occupation, or business that does not have its disadvantages and moments of boredom, be it burglary, tight-rope walking, preaching, or banking—or even professoring in a large teaching hospital where unusual cases abound, of which Dr. Tabrah seems to be so fond.

There can be no doubt that pediatric practice sometimes approaches the point where the pediatrician wonders if he will ever see anything again except run-of-the-mill colds, inoculations, and "checkups." He certainly will, and if he has been in practice for any length of time and goes over his records, he finds that he has seen about every disease that children have.

Pediatrics will continue to be a legitimate specialty because, although the pediatrician is the child's family doctor, and is in this sense a general practitioner, innumerable problems arise which are not seen in the adult, for the child is not merely a small man. He is a different *sort* of man, with his own private and particular troubles, many of which need, in order to be dealt with successfully, special knowledge which the general practitioner does not have. I fail to see how Dr. Tabrah can think that the practice of pediatrics is narrow, or that general practice will furnish more interesting problems.

It is true, as he has said, that the pediatrician has to see a large number of patients each day in order to make a good living. This won't hurt him; so does every other doctor except a surgeon. The practice of medicine has never been an *easy* way to make a living. There is, however, one great disadvantage in the pediatrician's life, from which he suffers more than any other doctor—the telephone. He is at the mercy twenty-four hours a day of as many women as comprise his clientele; he is continually interrupted at whatever he may be doing to talk of things which often amount to nothing. But life can't be all cakes and ale, no matter how one earns his living, and there really is not too much else in the pediatrician's business that incommodes him a great deal.

Dr. Tabrah says: "A few years ago this colorless job [the practice of pediatrics] was relieved by challenges of frequent and severe disease, and the physician was called upon to use his greatest ingenuity." To most people there is certainly nothing "colorless" about children, and it has always seemed to me that a pediatrician has to use a pretty considerable amount of ingenuity and wit every day of his life, whether or not he is dealing with serious diseases. Dr. Tabrah seems to think that there is satisfaction only in dealing with unusual cases, or in being shut up within the ivory towers of a big teaching hospital. This is not so for most people, and I can assure him from a long experience in a big teaching hospital, and also as a plain "house-to-house" doctor, that there is as much tiresome routine in a teaching hospital as there is in the "outside" practice of pediatrics.

I agree with Dr. Tabrah that some men are unfitted for pediatric practice because of individual tastes and personalities: this is not unnatural; there are plenty of young men in all occupations who get into the wrong job.

I know well at present two relatively young men who practiced pediatrics for a while—didn't like it—and are now working in research laboratories in a big hospital where they have both already done outstanding work, and will undoubtedly accomplish much

more before they are done. Each has found his proper place. The practice of pediatrics was not it.

If a man does not have a great liking for children, it is best that he keep out of pediatrics. This may be Dr. Tabrah's trouble. To most pediatricians there is something about a child that is appealing in the highest degree. I think that most of us have not just a *liking* for children, but a genuine love for them—for their freshness, their simplicity, their sheer beauty, their helplessness. Is there anyone more deserving of help than a child in trouble? Can a man occupy himself better than in trying to get him out of it? I doubt it.

LEWIS WEBB HILL

BOSTON, MASS.

News and Notes

Fellowships in developmental diagnosis are available at the **Clinic of Child Development** which is sponsored jointly by the Department of Pediatrics of the Ohio State University, College of Medicine, the Children's Hospital of Columbus, Ohio, and the State Department of Mental Hygiene and Correction. The Clinic is concerned with the evaluation of neurologic status and maturity level in children in the preschool period suspected of having deviations in development. The majority of the children have neuropsychiatric disabilities which are organic in nature. In addition to diagnostic evaluation, guidance in the management of problems, and help in securing the necessary medical and community services is provided.

Fellowships are open to pediatricians, or psychiatrists who are board eligible. They are for a period of one year beginning July 1, 1958, with one position each six months available, and carry a stipend of $5,000. Physicians who are trained will have opportunities to engage in research projects designed to elucidate the etiologies of the neuropsychiatric disabilities of childhood and to enter into the teaching program.

Address inquiries to: Dr. Earl H. Baxter, Chairman, the Department of Pediatrics, The Ohio State University, or to Dr. Hilda Knobloch, Director of the Clinic of Child Development, at the Children's Hospital, 561 South 17th Street, Columbus 5, Ohio.

Dr. Harris D. Riley, Jr., has been appointed chairman of the department of pediatrics at the University of Oklahoma School of Medicine, Oklahoma City. Dr. Riley was formerly on the staff of the pediatric department at Vanderbilt University School of Medicine.

The *Summer Camp for Diabetic Children* will be conducted for the tenth year under the auspices of the **Chicago Diabetes Association**, July 20–August 10, at Holiday Home, Lake Geneva, Wis. Boys and girls 8-14 years of age are eligible.

As in previous years, the camp will be staffed by resident physicians, a nurse, two dietitians, and a laboratory technician, in addition to the regular counseling and domestic staff of Holiday Home.

Rates for Summer Camp are arranged in accordance with individual circumstances. Applications may be obtained from, and inquiries should be addressed to: The Chicago Diabetes Association, 5 South Wabash Avenue, Chicago 3, Ill. (ANdover 3-1861.)

Applications for the residency from Jan. 1, 1959, to Dec. 31, 1959, in Pediatric Oncology at **Memorial Center for Cancer and Allied Diseases** in New York will be received up to July 1, 1958. This residency is approved for partial credit by the American Board of Pediatrics and is limited to the neoplastic diseases of children. Salary: $4300 annually plus maintenance. For application forms and information write: Director, Pediatric Service, Memorial Center for Cancer and Allied Diseases, 444 East 68th Street, New York 21, N. Y.

The **IX International Congress of Paediatrics** will be held in Montreal, Canada, from July 19-25, 1959, under the auspices of the International Paediatric Association at the invitation of the Government of Canada and the Canadian Paediatric Society. The scientific program has been planned to embrace the problems of child care in their broadest sense, and will include plenary sessions, panel discussions, original communications, and scientific exhibits. Simultaneous interpretation will be employed for all plenary sessions. Official languages will be English, French, and Spanish. A varied program of social events will be offered. The Preliminary Program and registration forms will be distributed in a few months' time to paediatricians throughout the world.

Medical Education Week, with the purpose of focusing the attention on, and informing the public of, the basic significance of medical education, will be held the week of April 20 to 26, 1958.

The **Seventh Annual Clifford D. Sweet Seminar,** sponsored by Children's Hospital of the East Bay, will be held on May 16 and 17, 1958, at the Claremont Hotel in Berkeley, Calif. Guest speakers will be: James G. Hughes, M.D., Professor of Pediatrics and Chairman of the Department of Pediatrics, University of Tennessee Medical School, and Paul H. Holinger, M.D., Professor Broncho-Esophagology, University of Illinois and Children's Memorinl Hospital.

Books

The Normal Child. Ronald S. Illingsworth, M.D., F.R.C.P., Second Edition, Boston, Little, Brown & Company, 1957, 356 pages. Price $7.00.

As a general rule, reviews of second editions are limited to pointing out important changes. We are under the impression that this text, by the Professor of Child Health at the University of Sheffield, is not well enough known to practitioners, in the United States at least, although the fact that the first edition, published in 1953, had to be reprinted the following year testifies to its general acceptance. This second edition, moreover, has been completely rewritten and extended in scope to cover the first five years. It is rather a unique book, and we are not familiar with any other text that covers quite the same ground, or has the same purpose. Some quotations from the preface of the first edition describe the author's approach and the scope of the text.

> "In some teaching schools there is too much emphasis on the rare and 'interesting' and too little emphasis on the common conditions which form the large bulk of family practice. In the case of children, many of these common conditions consist of variations from the normal which hardly amount to disease, but which cause a great deal of anxiety to the parents. The doctor may leave the medical school ill-equipped to deal with them." "It is because I felt this knowledge of the normal is not easy to acquire from the available text books that this one was planned." "In planning the book I was constantly faced with the difficulty of deciding what is normal and what is abnormal, and what, therefore, should be included in the book and what excluded. It is almost impossible to define the normal. It is certainly not synonymous with the average. A child may differ very widely from the average child in physical and mental development and yet be perfectly normal." "Behaviour problems are included in the book because every normal child has them. I feel that a child with no behaviour problems would be highly abnormal."

The author has very ably accomplished the task he undertook. He has arranged his material in four sections: Feeding Problems; Physical Problems; Developmental Problems; and Behaviour Problems (parental attitudes, discipline, sleep, anorexia, crying, etc.). There are a number of more extensive texts on each of these subjects, but by bringing them together in this way in relation to the normal child, a practical book which should be of great value to the practitioner has resulted. The book also is very well written and the discussions make interesting reading. The author shows a wide knowledge of the work and opinions of others concerning the topics discussed, and there is a bibliography running to 468 references. These, however, are not simply quotations but are woven into the discussions based on Dr. Illingsworth's experience.

The text should be of particular value and service to the younger pediatricians starting practice, as most of the problems he will encounter so frequently in pediatric practice, outside of the management of illnesses, are included. The book was of particular interest to the reviewer in connection with the recent criticism of the pediatrician as not being prepared by his training for the problems he will meet in practice and thus finding pediatric practice "unrewarding," which has been the subject of considerable discussion in the JOURNAL in recent months. From this viewpoint alone, the book can be read with great profit by the hospital residents planning to enter practice, as well as by their teachers. It is highly recommended for the practitioner's library.

B. S. V.

Tuberculosis: Every Physician's Problem. J. Arthur Myers, M.D., Springfield, Ill., 1957, Charles C Thomas, Publisher, 290 pages.

Rarely has an author been able to cover a subject of so wide a scope, as concisely

and yet as completely, as has Dr. Myers in this splendid work on tuberculosis. The book is divided into three parts. The first includes a brief but comprehensive historical sketch, a discussion of the bacteriologic characteristics of the tubercle bacillus, and a description of the invasion and pathogenesis of primary tuberculosis. In the second part a thorough discussion of the clinical (reinfection) type of tuberculosis is given, including its pathogenesis, diagnosis, and present methods of treatment. An excellent evaluation of the specific drugs presently in use is given in this section. The third part of the book deals with control to eradication, in which, after a brief consideration of the many anachronisms that were once somewhat widespread and have since been abandoned, a careful evaluation is made of the control measures that have been used. The role of the physician in the program for control and eradication of the disease is thoroughly discussed. Finally, the author cautions against the danger of overconfidence, built up by the somewhat phenomenal gains that have been made, and warns that a lessening of the intensity of the present efforts toward control and eradication of the disease could easily result in wiping out all of the beneficial progress made thus far.

The book gives a complete account of present-day knowledge of the disease and its treatment today and should be of interest to every practicing physician, regardless of his specialty.

D. S.

Practical Allergy. M. Coleman Harris and Norman Shure, Philadelphia, 1957, F. A. Davis Company, 471 pages.

Concise, well written, and well printed, this textbook will be of help to any physician, but of the greatest usefulness to the one who has had little or no training in the care of allergic patients. It should also provide an excellent introductory work for medical students. The text is readable. The views expressed are sound. Controversial issues are well handled. The importance of individualizing each case is emphasized.

The pollen chart for the United States may be a little awkward to use. The plant pictures are good, but the list is not complete for some parts of the country. The investigation of environmental factors is well presented but the procedures of environmental control are not.

Many pediatric allergists would object to giving cod-liver oil to allergic infants as the authors recommend and would prescribe instead the crystalline form of the vitamins A and D.

Consideration should be given to the type of infecting organism before prescribing antibiotics to the patient having asthmatic bronchitis.

The authors are to be commended for their very sane presentation of the use of steroid medication.

The book, as its name implies, is concerned with the practical aspects rather than the theoretic aspects of allergic disease. It contains enough of pediatric interest and importance to recommend its use by any practicing pediatrician.

G. B. L.

Barbara. A Prologue. Willard Abraham, New York, 1958, Rinehart & Co., Inc., 94 pages. Price $2.00.

One of Those. Sophia Gant, New York, 1957, Pagent Press, Inc., 88 pages. Price $2.50.

These are two small books for lay reading, by parents to whom children with mongolian idiocy were born, published within a few weeks of one another. Except for the subject they have nothing in common. The author of *Barbara* is a professor of education at a southwestern state university and by the irony of fate was particularly interested in exceptional children. The infant was placed in an institution for retarded children and lived a relatively short time. It is very well written and the story is one of the emotional reactions of the parents following the birth of the infant and their adjustment to the calamity.

It is not so easy to review Mrs. Gant's book. In this case the child, now around 20 years of age, obviously belongs in the group of mongols with minimum retardation. His mother, a former teacher, has devoted her life to his education with remarkable results. A printed sample of a week's schedule or "time table" at grade 7 is amazing. The

book is a revelation of what a devoted, never discouraged mother, acting as a teacher, can do. The difficulty in reviewing the book objectively lies in the fact that Mrs. Gant is a deeply religious woman and attributes all of her son's progress and development as God's answers to her prayers, and never in any way to her own work. The book is replete with biblical references on almost every page. Far be it from the reviewer to enter into a discussion of the reasons for the boy's progress. She has accomplished a remarkable achievement and is entitled to her viewpoint and opinion.

B. S. V.

Child Psychiatry. A Thoroughly Reliable Guide to Children's Behavior Problems, ed. 3. Leo Kanner, M.D., Springfield, Ill., 1957, Charles C Thomas, Publisher, 777 pages. Price $8.50.

The third edition of Kanner's *Child Psychiatry* maintains the high standards set by the earlier editions. Many sections have been extensively rewritten. The new edition can be relied on for the inclusion and critical evaluation of recent advances in child psychiatry.

The book is unique among textbooks. Kanner has thought widely about his field. The treatment of each subject reflects his deliberations. He accepts nothing without first weighing it—and then, if he accepts, he accepts tentatively. Yet the reader does not find himself confused by this way of presentation. Rather it leads to clarification.

Kanner writes easily, at times almost conversationally, often with quiet humor, always with great humanity. Psychiatric terms whose meaning might be obscure to the pediatrician are, in the main, avoided.

For the pediatrician—as well as the child psychiatrist—this book should be invaluable. The field is comprehensively covered and a well-selected bibliography is available at the end of each chapter for those who would go to original sources or who want to dig deeper.

H. B.

Laboratory Applications in Clinical Pediatrics. Irving J. Wolman, M.D., New York, 1957, McGraw-Hill Book Company, Inc., 1019 pages.

This book is a comprehensive summary of laboratory procedures which are useful in the practice of pediatrics. The author reviews the normal values for each test according to age, but does not present any methodology except when this knowledge is necessary for obtaining the proper test sample.

The application of the laboratory procedures are discussed in light of the pathologic physiology of the various diseases. The indexing and organization of the book enable the reader to study the application of a single laboratory test or to determine what procedures should be carried out for accurate evaluation of a certain disease. Frequently, the author summarizes the accepted therapeutic regimes and relates the clinical response to this therapy to the changes in laboratory determinations.

This book is not a laboratory manual, but is a discussion of pathologic physiology as shown by routine laboratory tests. It should be a worth-while addition to the library of all persons and institutions interested in the treatment of infants and children.

M. R. B.

Editor's Column

DO WE NEED A NEW PERSPECTIVE IN INFANT NUTRITION?

HAND in hand with the nutritional scientist, the pediatrician has striven for the betterment of nutritional health in our society. The development of the deficiency concept of disease provided a guiding philosophy for this effort, the discovery of the various essential dietary factors a verification of important hypotheses, modern food technology the implementary tools. This grand coalition of effort—scientific, agricultural, commercial—has in the short span of half a century wrought a nutritional revolution.

Not all societies have participated in this revolution. There is still much concern over the welfare of the millions of starving children inhabiting large sections of the globe. This and other considerations have conspired to preserve the deficiency concept as paramount in the nutritional field. For the most part, our students are taught in terms of minimum requirements. Strenuous efforts are being made to show that a number of diseases of uncertain etiology represent deficiency states. Despite our surfeit of food we are being urged to eat more and more. The casual observer easily gains the impression that our society could be still better fed.

But *medicus, circumspice!* The results of the nutritional revolution are plainly visible. Clear-cut examples of deficiency states are difficult to find for purposes of classroom demonstration. Well-nourished children fill your offices. Malnutrition is no longer a major problem in those areas of our country where good medical care is enjoyed.

Perhaps the time has come for an examination of the following question: In our zeal to prevent nutritional deficiencies in the infant and child population have we actually succeeded in feeding them too much? Sparse though they are, the inferential data pertinent to this question are deserving of consideration.

Nutritional excesses can be harmful. The suggestive relationships between dietary fat and atherosclerosis, and between salt intake and hypertension are attracting the attention of the physician who cares for adults. The health experience of life insurants indicates that an optimal weight exists for the adult, for there is a modest increase in mortality for those who are underweight and a striking increase for the overweight. In the experimental animal the case against overfeeding has been documented for a number of species. Of interest to the pediatrician is the inverse relationship between growth rate and longevity which has been noted in widely divergent species, and many years ago Raymond

Pearl concluded that "the length of life depends inversely on the rate of living."

Overnutrition in the adult is fast assuming the status of a major nutritional problem. Whether obesity in the child constitutes a threat of similar magnitude is a question which cannot be answered on the basis of present evidence. However, Hilde Bruch's observations have shown that the obese child tends to remain overweight in adult life. Despite the lack of precise data on this point, the observations on adults together with the results of animal experiments point to the desirability of reassessing childhood nutrition and current nutritional practice in the modern perspective.

A particularly compelling consideration is to be found in the established trend in the growth performance of infants and children. There is ample evidence that the infant and child of today are growing faster than in previous generations. Standard growth charts need periodic revision, and always in the upward direction. This is not an isolated phenomenon, for it has been recorded by Meredith for this country, by Tanner and Morant for England, Norway and Germany, and by Ebbs for Canada. Children of all ages, save the newborn, have shown a progressive increase in height and weight in successive generations. Maximum height in the male is attained at an earlier age. Both sexes have shown this change, and all economic groups are involved. During this same period, which covers about a hundred years, there has been a progressively downward trend in menarcheal age, and the age at which the adolescent growth spurt occurs.

The reason for this trend is not known, nor is it known whether it extends back beyond the mid-nineteenth century since systematic observations on human growth rates were not made prior to that time. Possible explanations include the progressive hybridization of the western races and the decline in chronic intercurrent disease. Some have speculated that it is merely a phenomenon of recovery from the ravages of the early phase of the industrial revolution. Observations such as the dips in the secular curve during wartime in Europe and the economic depression and the fact that obese children show advanced stature and maturation strongly suggest that improved nutrition is in part responsible.

The question may now be posed: What is optimum growth? Basic to this consideration is the fact that all human growth data are empirical. On a priori grounds there is no way of deciding whether the child of yesteryear was stunted, or the one of today overgrown and overnourished. Nor can we conclude without further evidence that the observed changes in growth pattern have been wholly beneficial, as many would have us believe.

The requirements for many dietary essentials are geared to growth rate, so the definition of optimum nutrition is bound up with the one above. Despite the valiant efforts of nutritionists it must be admitted that precise information on the matter of minimum requirements is lacking for all but a scant few of the essential constituents of the diet. The tendency has been, on the part of physician and official council alike, to err on the side of recommending too much rather than too little. The gaps in knowledge here have been recently highlighted,

for example, by the discovery that children in Ceylon appear to thrive on an intake of calcium considerably below that supposedly necessary for the American child. Outside of certain disease states, we know very little about possible variations among children in their dietary needs.

In view of these uncertainties in our knowledge, should we continue to give concentrated formulas to infants, formulas which supply much more protein, calcium, and calories than the usual breast-fed baby receives? Should we foster the earlier and earlier introduction into the infant diet of solid foods for which there is no proved need? Should we continue to condone among the parents of our patients the attitude that bigger babies are better babies? In the light of recent reports of the deleterious effects of modest increases in vitamin D and vitamin K dosages, should we not take another look at current practices in prophylactic vitamin prescriptions?

At the dawn of modern pediatrics there were many forces at work in the direction of undernutrition. These are still in effect in many areas of the world, but today in our society they have been largely replaced by forces operating to promote overnutrition. The decline in intercurrent chronic disease is one such force. Another is modern food technology: the improved digestibility of modern artificial formulas, the tremendous production of high-quality foods, the speed with which foods can be distributed among our people, and the efficiency with which they are protected against deterioration during storage are all important factors. Highly potent dietary supplements are available in increasing quantity: the commercial production of vitamins has risen 700 fold in the last 17 years, and the annual output can now be measured in tons. Promotional advertising is aimed at increasing the desire for even more food. Overnutrition is easier to achieve than at any time in the past. To a large extent it will be the actions of the pediatrician as observer and counsellor which will determine whether it will constitute a threat to the child of the future.

GILBERT B. FORBES

INFANT FEEDS—HOT OR COLD?

IN THIS issue (page 404) we publish a report that has been of considerable interest to the Editorial Board for a number of reasons. By its publication it should not be assumed that the JOURNAL and the members of the Board advocate discarding the time-honored custom of warming the bottle before offering it to the baby. Dr. Gibson, of Abilene, Texas, whose intellectual curiosity led him to question the importance of strict bed rest for children with minor febrile diseases (J. PEDIAT. 49:256, 1956) has questioned the importance, or better, perhaps, the necessity, of another time-honored custom. Many pediatricians will recall isolated experiences in their practice where babies have been fed unwarmed bottles without apparent harm. Such an experience led Dr. Gibson to investigate the use of unwarmed

feeds by a study conducted in his private practice. Eighty-nine per cent of 150 infants accepted cool or cold formulas, and, in 120 of these followed, development proceeded normally. No harmful effects were noted.

Thus the importance of another time-honored custom has been questioned by an "inquiring mind." One of the reasons for its interest is that it is a study based on material in a private practice, in the way so many advances have been made, of which the work of Mackenzie in cardiology is a brilliant example. Further, it was made without the use of a laboratory, although it raises questions that require laboratory investigation. For example, some laboratory worker may be interested enough to determine by means of a thermocouple the temperature of the cool milk by the time it reaches the stomach, and such questions as to whether a cool feeding influences the secretions and peristalsis: studies we doubt if Dr. Gibson is in a position to carry out.

Another reason for its interest, as one member of the Board who reviewed the manuscript remarked, is that it is a warming refutation of the lack of rewards of the private practice of pediatrics—a subject of much discussion by JOURNAL readers since the publication of the letter by Dr. Tabrah last December. We are quite certain that Dr. Gibson has found the private practice of pediatrics in a small city not only completely rewarding, but of exciting interest. There is an old saying, full of truths, that what a man gets out of anything depends upon what he puts into it.

DIET LISTS

IN Professor Illingsworth's recent book, *The Normal Child*, reviewed elsewhere in this issue by the Editor, a paragraph under the heading, "A little knowledge of nutrition" brought recollections of one of the several episodes in pediatric practice when our zeal ran ahead of our knowledge and experience, as so often has happened in medicine. I refer to the handing out to parents of "diet lists" with elaborate details as to the different foods and the exact amounts to be given to children at each meal. It had its genesis to a large extent in the great interest in malnutrition in children that developed some 40 to 50 years ago. This diagnosis was largely based on finding that a child fell below the average of the weight-height-age tables obtained from the measurements of thousands of children of school and preschool age. If a child was a small percentage below the average, he was classified as "malnourished," and steps must be immediately taken to improve his diet. So diet lists became a vogue and were given much lay and medical publicity. The intent was to instruct parents and make it easy for them to give Johnny three well-balanced meals a day, thus providing sufficient calories in desirable amounts of protein, fat, and carbohydrate to prevent malnutrition.

Everyone got into the act. Pediatricians were considered as neglecting their duties if they did not place tremendous stress on the importance of diet. The manufacturers of prepared

foods soon had their nutritionists prepare elaborate and attractive diet lists furnished gratis to the doctors to hand out to parents. (Of course there was a joker—introduced into the breakfast, for example, "2 tablespoons of X's sawdust.") There were many conferences and committee meetings held to discuss diets and diet lists, and what should be included and excluded. I recall one held by the Children's Bureau which was preparing a government "hand out" of diet lists. The subject at the moment was what green vegetables should be included besides spinach, and finally cabbage was reached. One of our distinguished colleagues from Boston spoke up in horror. "*Cabbage!!* cabbage for a child, it's impossible. Who ever heard of giving cabbage to a child!" Then a pediatrician from the southeastern section of the country spoke up quietly, "Well, all I've got to say is that if cabbage is not included in the list most of the children in my part of the country won't get any green vegetables." Cabbage was included.

So with the best of intentions diet lists became a great achievement in the modern pediatrics of that period. On starting private practice in 1919 one of my first steps was to prepare an elaborate set of diet lists for children of different ages to be given to parents, and in which considerable pride was taken.

Then the troubles began. Mothers were led to feel that as it was all very scientific, and that if they did not follow the list to the last detail and if they did not see that every last morsel of the indicated amount was consumed at each feeding, the child's health and growth would be in serious danger. In despair, trying to accomplish the impossible, the mother would try persuasion and bribery, then threats, and finally punishment. Mealtime became a "field day" for behavior, enabling the children to gain attention and get their own way. Perfectly capable mothers were made to feel that they were incompetent and were failures as mothers. The entire life of the family became upset, trying to carry out the children's diets prescribed by their doctor. It did not take long for the pediatricians to wake up to the fact that the most important problem was one of attitudes toward food, rather than the rigid detailing of so much of this and so much of that. The implications of the study of Clara Davis in Brennemann's clinic in Chicago was the final push to reality. Some five years after starting practice, with great benefit to both mothers and children, all the diet sheets in my office were torn up, with the exception of those for special conditions such as obesity and for certain diseases where the diet is an important part of the treatment.